MICROBES ON THE MOVE

INFECTIOUS DISEASES IN ASYLUM SEEKERS

SCREENING AND VACCINATION POLICIES

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COLOPHON

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PART II. SCREENING AND VACCINATION POLICIES

01

General introduction

Recent migration trends

In 2011, the Syrian civil war started which led to turmoil and instability in Syria and the surrounding countries in the Middle East. The United Nations High Commissioner for Refugees (UNHCR) estimated that more than 5.7 million Syrian people fled the country and more than 6.1 million people have been displaced internally from 2011 up to date[1]. The Syrian conflict, but also continuous unrest in other areas in the Middle-East, Asia and Africa[2,3], forced millions of people to flee their home land. During the last decades, the number of forcibly displaced people was estimated around 40 million people each year. In 2018, the population of forcibly displaced people grew up to 70.8 million[3]. This increase was most significant between 2012 and 2015. Over 1 million people tried to reach Europe in 2015 alone. People mainly originated from Syria (4.9 million) and Afghanistan (2.7 million)[4], leading to the highest increase of migration that Europe had faced since the Second World War. Nowadays, the number of refugees trying to reach Europe has declined compared to 2015. However, considering the political instability of areas like the Middle-East or Africa, the number of refugees will fluctuate in the years to come.

Migration and health care challenges

In an attempt to reach European shores, different routes are taken by refugees. The European Border and Coast Guard Agency, also known as Frontex, reported seven active routes, namely[5]:

1. Eastern land borders
2. Western Balkan
3. Circular route from Albania to Greece
4. Black Sea
5. Central Mediterranean
6. Western Mediterranean
7. Eastern Mediterranean

The Western Mediterranean and Eastern Mediterranean route are considered as the most active routes at the moment and are reported to have the highest number of border crossings. In 2018, the numbers of border crossings reported for both routes are 57 034 and 56 561 respectively. Via the Western Mediterranean and the Eastern Mediterranean route, refugees mainly arrive in Spain and Greece while Italy has to deal with a high number of refugees trying to enter the country through the Central Mediterranean route. The Central Mediterranean route used to be one of the main migration routes to the European Union/European Economic Area (EU/

EEA). However, since the start of an active policy of the Libyan Coast Guard in the summer of 2017, the number of border crossings declined with 80%. In 2018, 23 485 border crossings were reported. This is the lowest number since 2012[6].

Based on the Dublin regulation (regulation no. 604/2013), an EU Member State is obligated to evaluate asylum claims after arrival in Europe. This obligation generally attributes to the Member State that plays the most significant role after initial arrival in Europe and aims to guarantee a quick asylum procedure for every refugee[7,8]. In practice however, this results in an enormous responsibility in terms of registration of these people for receiving countries like Italy and Greece.

According to article 12 of the International covenant on Economic, Social and cultural Rights (ICESCR), every person is entitled to health care. This right is phrased as follows:

> *"the right of everyone to the enjoyment of the highest attainable standard of physical and mental health".*

The key to the right to health contains two aspects; freedom and entitlement. Freedom includes consensual and informed healthcare. Entitlement indicates the obligation of the state to provide adequate health services, protection, access to information and education and sexual and reproductive health-care services[9]. This poses a challenge for local health care systems and healthcare workers within Europe to provide adequate health services for everyone in order to fulfil this obligation. Besides the responsibility of every European member state to provide adequate health care levels, refugees also face multiple barriers that withhold them from accessing health care. Barriers that have been reported are mostly considered to be language and cultural differences, discrimination and costs[10–12]. Another challenge regarding healthcare for refugees is the fear of detection, detention or deportation after seeking medical treatment. However, barriers may vary from country to country[10].

Migration and multidrug-resistant organisms

Multidrug-resistant organisms (MDROs) are defined as organisms that are resistant to one or more agents in at least three or more antibiotic classes. Methicillin-resistant *Staphylococcus aureus* is always considered as an MDRO regardless of the co-resistance in other antibiotic classes[13]. The epidemiology of MDROs within European countries varies significantly[14]. A closer look into the epidemiology of MDROs within Europe as reported by European Antimicrobial Resistance Surveillance Network

(EARS-Net) reveals a striking difference regarding the prevalence of MDROs within the EU[15]. For example, a prevalence of 6.2% for extended-spectrum β-lactamase-producing *Escherichia coli* is found in the Netherlands compared to 29.5% in Italy. The prevalence of carbapenem resistant *Klebsiella pneumonia* in the Netherlands and in Greece is 0.5% and 64.7% respectively[16]. Travelling and migration are known factors in the spread of MDROs. The transnational journey and crowded conditions in refugee camps or settlements are considerable factors in the dispersion of antimicrobial resistance among this vulnerable group. Possible introduction of MDROs in Europe could have consequences for subsequent screening procedures that are needed in low prevalence countries like the Netherlands.

Migration and infectious diseases

Besides MDROs, migration may lead to the introduction of infectious diseases that medical professionals in Europe are less familiar with. As an example, in July 2015, a patient from Eritrea who just arrived in the Netherlands was admitted to a regional hospital in the northern Netherlands with complaints of headache and fever. Malaria was suspected but could not be diagnosed. The patient received ceftriaxone as empirical therapy. As a reaction the patient's situation deteriorated within hours and the patient had to be admitted to the Intensive Care Unit at the University Medical Center Groningen (UMCG). Later, louse borne relapsing fever caused by *Borrelia recurrentis* was diagnosed[17]. A second case occurred only one week later, but was directly referred to the UMCG. Additional cases of louse borne relapsing fever were reported in Switzerland in August 2015[18] and Italy in September 2015[19]. In the following months, at least 40 confirmed *Borrelia recurrentis* cases were reported in Germany[20], one case in Belgium[21], and two cases in Finland[22]. The two cases in the UMCG initiated the work presented in this thesis. The patients demonstrated the urgency to further investigate infectious diseases observed in asylum seekers who are referred to the hospital.

In addition to the introduction of infectious diseases unfamiliar to European medical professionals, a second challenge in migrant health is the protection of migrants against infectious diseases. As migrants originate from countries where healthcare systems have been inadequate for years, vaccination rates are expected to be insufficient. An adequate tool to reduce the burden of infectious disease is to ensure adequate vaccination rates among migrants. In order to guarantee adequate vaccination rates, a European approach is needed to organize vaccination of migrants on a European level. Moreover, due to the crowded condition during their journey to Europe and in settlements, outbreaks of communicable diseases

also occur, mainly affecting unvaccinated migrants[23–25]. An example is a scabies outbreak in a settlement in Calais in 2014. Such outbreaks require a quick response to contain the outbreak now and in the future.

The asylum procedure in the Netherlands

The Netherlands has a centralized system of asylum requests. Apart from a small minority arriving at the national airport Schiphol, the majority of asylum seekers has to apply for asylum at the national registration centre of the Immigration and Naturalisation Service (IND). These centres are located in Ter Apel in the north-eastern part of the Netherlands or in Budel in the Southern part of the Netherlands. Asylum seekers stay for a maximum of 72 hours at the national registration centre. Here, the Aliens Police conducts an identity check and all personal data is registered. After registration, asylum seekers are screened for active pulmonary tuberculosis by the Public Health Service Groningen (GGD). Chest radiography is used as a standard screening tool in The Netherlands and is mandatory for all asylum seekers over six months old. Asylum seekers who originate from countries with a tuberculosis incidence of less than 50 cases per 100000 inhabitants are excluded from the screening (e.g. asylum seekers originating from Syria)[26,27]. In case the chest X-ray is suggestive of intrathoracic tuberculosis, further diagnostic procedures are performed by the tuberculosis department of the regional Public Health Service Groningen, or by the UMCG. Eventually, treatment is started by the GGD Groningen or the UMCG. After 72 hours at the national reception centre, asylum seekers are transferred to one of the asylum centres in the Netherlands to wait for the processing of their asylum application.

Aims and outline of the thesis

The overall goal of the thesis is to improve the knowledge regarding the epidemiology of MDROs among asylum seekers and to evaluate current screening and vaccination procedures in the Netherlands and Europe. Therefore, the aim of the work presented in this thesis is twofold. Part I of this thesis aims to investigate the prevalence of MDROs in asylum seekers in the Netherlands, the duration of carriage of MDROs and the possible consequences for screening procedures. This introduction, **Chapter 1**, describes the migration trend over the last few years. It describes the challenges in the provision of health care for refugees and the asylum procedure in the Netherlands. **Chapter 2** shows the prevalence of infectious diseases and MDROs from asylum seekers admitted to the UMCG. **Chapter 3** provides more insight into the prevalence of MDROs in asylum seekers, focussing on the north-eastern part of the Netherlands. The prevalence of MDROs is compared to the

prevalence of MDROs in the general patient population in the Netherlands. **Chapter 4** discusses the duration of MDRO carriage in the asylum seeker population after arrival in the Netherlands. **Chapter 5** investigates if transmission or outbreaks of ESBL-producing Gram negative bacteria have occurred amongst asylum seekers either during the travel to Europe or during their stay in the asylum seeker centre by the use of whole genome sequencing.

Part II of this thesis focuses on different screening and vaccination programmes within the Netherlands and Europe. **Chapter 6** evaluates the scabies programme that was introduced in the national reception center in Ter Apel in order to reduce the number of scabies cases reported. **Chapter 7** describes the potential of mass drug administration to reduce the burden of scabies in refugee settings. **Chapter 8** and **Chapter 9** focus on the vaccination programmes for recently arrived refugees in the EU/EEA countries. First, a policy analysis is performed across all countries to compare national approaches. Subsequently, national experts across all EU/EEA countries completed a survey to evaluate current approaches on the vaccination of refugees. **Chapter 10** aims to investigate refugees' perspectives on infectious diseases screening and vaccination policies. **Chapter 11** summarizes all the results of this thesis. **Chapter 12** discusses the results and the future perspectives.

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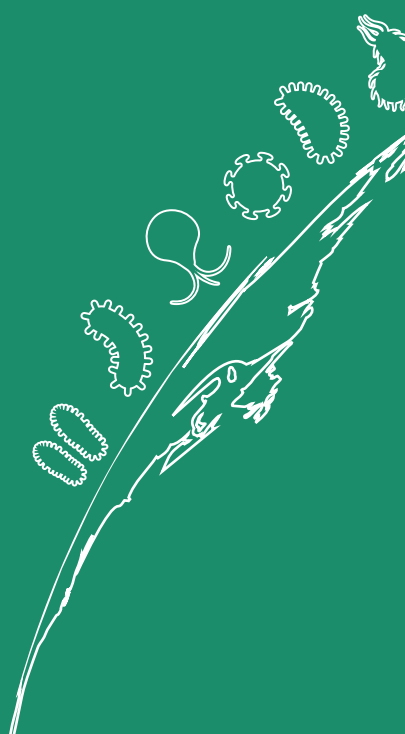
PART I

Multidrug-resistant organisms in asylum seekers



02

High Prevalence of Infectious Diseases and Drug-Resistant Microorganisms in Asylum Seekers Admitted to Hospital; No Carbapenemase Producing Enterobacteriaceae until September 2015

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ABSTRACT

Introduction

The current refugee crisis emphasizes the need for information on infectious diseases and resistant microorganisms in asylum seekers with possible consequences for public health and infection control.

Materials and Methods

We collected data from asylum seekers admitted to our university hospital or who presented at the Emergency Department (n=273). We collected general and demographic characteristics including country of origin, the reason of presentation, and the screening results of multidrug-resistant organisms (MDROs).

Results

67% of the patients were male with a median age of the study group of 24 years (IQR 15-33); 48% of the patients had an infectious disease – predominantly malaria with *P. vivax* or tuberculosis. Patients also reported with diseases which are less common - e.g. leishmaniasis, or even conditions rarely diagnosed in Europe – e.g. louse borne relapsing fever. A carriage rate of 31% for MDRO was observed, with ESBL-expressing *E.coli* (n=20) being the most common MDRO. No carriage of Carbapenemase Producing Enterobacteriaceae was found.

Conclusion

The current refugee crisis in Europe challenges hospitals to quickly identify and respond to communicable diseases and the carriage of MDRO. A rapid response is necessary to optimize the treatment of infectious diseases amongst asylum seekers to maximize infection control.

INTRODUCTION

The current refugee crisis in Europe challenges both society as a whole and health care workers. Six hundred and twenty-six thousand people applied for asylum in the 28 European (EU) Member States in 2014. When compared to 2013, this was an increase of 45%[1]. More than 350,000 refugees reported at the EU borders between January-September 2015. This number may be an underestimate as many refugees may have remained undetected[2,3].

Next to travelling, migration is a well-known factor in the spread of infectious diseases and multidrug-resistant organisms (MDROs)[4]. However, little is known about the carriage of infectious diseases and MDRO in asylum seekers whenever they report with illness to the healthcare system in the host country with possible implications for hospital infection control.

The Netherlands have a very active surveillance for MDRO with a very low MDRO prevalence among patients admitted to hospital[5]. The overall carriage of extended spectrum beta-lactamase (ESBL) producing bacteria in the Dutch population is 5.1%[6]. In hospitals the overall carriage rate of vancomycin-resistant enterococci (VRE) is 0.4% and the percentage of methicillin-resistant *Staphylococcus aureus* (MRSA) is only 2%. Most cases of Carbapenemase-producing Enterobactereaceae (CPE) in the Netherlands have been reported in patients repatriated from a foreign hospital[7], although some hospital outbreaks have occurred[8]. The Netherlands has a strict hospital infection prevention policy, especially with respect to screening for patient admissions for those recently admitted to hospitals in foreign countries. Screening policy does not include travellers and it is currently unclear whether asylum seekers without a recent hospital admission would need to be screened.

In addition to the carriage of MDRO, asylum seekers may present with infectious diseases which may have consequences for public health and hospital hygiene; immigrants are known to have a higher rate of tuberculosis compared to the indigenous population[9,10]. However rates may vary considerably between countries of origin. The incidence of tuberculosis is 78 per 100.000 inhabitants in Eritrea and 17 per 100.000 inhabitants in Syria[11]. Information on MDRO carriage in countries of origin is scarce. In Syria the rate of MDR gram negative bacteria in selected patient populations with clinical infections was around 50-60%[12,13].

The spectrum of infectious diseases asylum seekers present with depends on risk factors such as country of origin, exposure during travel, previous living conditions, and access to health care and migration routes[14].

Here we report the spectrum of infectious diseases, prevalence of patients carrying MDRO's amongst asylum seekers who presented to the University Medical Centre Groningen which is located close to the national registration centre for asylum seekers in the Netherlands. Our data may conceivably help improve adequate care for asylum seekers with infectious diseases and enable optimal hospital hygiene strategies.

MATERIALS AND METHODS

Asylum seeking procedure in the Netherlands

In 2014 24,929 asylum seekers arrived in the Netherlands, an increase of almost 62% compared to 2013 (15,394). In the context of the current European refugee crisis, the number of asylum seekers in 2015 has increased considerably. Since January 2015 up until the beginning of September 2015, 33,598 asylum seekers had already reported at the national registration centre[15].

The Netherlands operate a centralised system of asylum application. Apart from a small minority at the national airport Schiphol and unaccompanied minors, the majority of asylum seekers must file their request at the national registration centre in Ter Apel. Within the first three days following arrival individuals are identified, registered and screened for active pulmonary tuberculosis. In Spring 2014 a standard preventative treatment of scabies was introduced. Screening is performed by the municipal health services. All asylum seekers are insured by the same insurance company and have an insurance number that starts with 9010 as decided by the insurance company. After this period, asylum seekers move to one of the asylum centres in the Netherlands to await processing[16].

Screening at admission to the hospital

The University Medical Centre Groningen is the university hospital closest to the national registration centre (60 km) and a preferred carrier for treating infectious diseases. The general practitioner based at the national registration centre decides whether the asylum seeker is referred to the regional hospital or the university hospital and for abnormalities found during TB screening the TB control physician in Groningen decides.

General infection prevention policy in the Netherlands includes screening for MRSA, VRE and resistant gram-negative bacteria of all patients who admitted to a hospital outside the Netherlands in the past 2 months.

In April 2014, the department of medical microbiology in the UMCG advised screening for MRSA, VRE, and multidrug-resistant gram negatives for all asylum seekers admitted to the hospital or who presented at the emergency department (with a high probability of a subsequent admission). This advice was only given if admission or outpatient visit was reported. The reason for screening was the anticipated high carriage rate of MDRO in asylum seekers when considering their countries of origin. Asylum seekers who were admitted or presented to the emergency department were screened for carriage of the following MDRO's: MRSA, ESBL, fluorquinolone- and aminoglycoside-resistant (MDR) Gram-negative bacteria, VRE, and CPE as part of standard care.

Carriage of MDRO does not have consequences for hospital hygiene measure in the outpatient setting. Therefore patients only visiting out-patient departments were not included in the MDRO screening.

Selection of participants

A retrospective study was conducted at the UMCG. All asylum seekers admitted to the UMCG or reporting to the emergency department between April 1st 2014 through September 1st 2015 were included. Patients were identified as asylum seekers based on their specific insurance number. Patients with the specific insurance number but whose asylum request was rejected by legal authorities as evidenced by the information available in their medical records were not included. Only asylum seekers who presented at the emergency department or who were admitted to the wards, or the tuberculosis department were included. If patients were admitted more than once, only the first admission in the study period was included.

General characteristics such as age at admission, gender, country of origin, and arrival data in the Netherlands, admission period and reason of admission were collected. Detailed information was collected concerning infectious conditions the patients presented with. The ICD-10 classification was used to describe the non-infectious diseases patients presented with at the hospital[17].

Screening for MDRO

Screening for MDRO consisted of swabs from nose, throat, rectum and perineum. MRSA was tested on nose, throat and perineum swabs with PCR (GeneXpert Cepheid). These swabs were also cultured on enrichment broth and chromID-MRSA plates (Biomerieux). VRE was detected as described previously [18]. Presence of MDR Gram-negative bacteria in throat and rectum swabs was detected by culture on selective agar plates (3-com Iso sensitest agar ME/CF/CX and CI/TO/PT, Mediaproducts, Groningen, the Netherlands). Antibiotic susceptibility was tested by automated susceptibility testing (VITEK2, bioMerieux, Marcy l'Etoile, France), or E-tests (AB Biodisk, Mannheim, Germany) applying EUCAST guidelines. Presumptive ESBL-, plasmidal AmpC-, or carbapenemase-producing isolates were analysed for presence of resistance genes by a DNA-array (Check-MDR CT103, Check-points, Wageningen, The Netherlands).

If patients tested positive they were isolated during their stay in the hospital, according to national and local guidelines. All patients diagnosed with TB or some patients suspected to have TB are referred directly to the UMCG tuberculosis centre and sanatorium Beatrixoord. This facility serves as one of the two national referral centre's for tuberculosis and is the largest designated tuberculosis centre in Europe. This study was evaluated by the ethics committee and was waived in accordance with Dutch legislation owing to its retrospective nature (University Medical Centre Groningen, METc number 2014/325). No written informed consent was obtained from patients for the use of retrospective data but patient information was anonymized and de-identified prior to analysis.

Statistical analysis

Data was collected in and analyzed with SPSS (version 2.22) and descriptive statistics were used for the diagnosis and MDRO screening results. Data is presented as mean (SD) or median with 25-75% inter quartile range (IQR) as appropriate. General data was obtained from the patients' file. When the date of arrival was only mentioned the year, either the 1st July or 1st of January was entered based on the information available.

The association between the number of days in the Netherlands and performing a screening for MDRO was calculated by Mann-Whitney-U test.

RESULTS

Study population and group characteristics

Between April 1st 2014 through September 1st 2015 care was provided to 736 asylum seekers in our university hospital. We included 273 patients who presented at the emergency ward or were admitted to the ward for further analysis. General characteristics can be found in Table 1. Most people originated from Eritrea (36.5%) or Syria (18.6%). Thirty-three (12%) asylum seekers were babies born in the Netherlands.

TABLE 1. General characteristics of asylum seekers admitted or presenting at the emergency department

	Number of asylum seekers
Male (%)	184 (67%)
Days in the Netherlands Median (IQR)*	74 (22-247)
Age median (IQR)	24 (15-33)
Country of origin	
Eritrea (%)	92 (36.5)
Syria (%)	47 (18.6)
Afghanistan (%)	8 (3.2)
Armenia (%)	21 (8.3)
Nigeria (%)	7 (2.8)
Other, Africa (%)	38 (15.1)
Other, Asia (%)	21 (8.3)
Other, Middle East (%)	12 (4.8)
Other, Europe (%)	5 (2)
Other, South America (%)	1 (0.4)
Missing (%)	21 (8.3)

**In 153 patients, arrival date in the Netherlands had not been recorded*

The median number of days in the Netherlands before presentation in the hospital was 74 (IQR 24-283). Many of the patients (32%) were admitted to the hospital or presented to the emergency department within the first 4 weeks after arrival in the Netherlands. Fourteen patients were admitted within the first week of arrival: 10

of whom were admitted within the first three days after arrival. In 56% (n=153) no arrival date was reported in the patient documentation. Patients were admitted for a median duration of 7 (IQR2-26) days.

Purpose of hospital visit

130 patients were admitted with an infectious disease of which 23% presented with vivax malaria (n=30) and 34% proved to have pulmonary tuberculosis (n=44). Three patients with pulmonary tuberculosis had drug resistant tuberculosis: one patient with MDRTB (from Georgia), one patient with XDRTB (from Latvia) and one patient with INH resistant pulmonary tuberculosis who originates from Syria but lived in both the Ukraine and Libya before seeking asylum in the Netherlands. 186 patients presented with non-infectious disease, with 22% (n=40) associated with pregnancy, childbirth and post-partum care, 11 % (n=22) with diseases of the circulatory system and 12 % with injury, poisoning and other consequences of external cause (n=21). The diseases asylum seekers presented with are described in detail in Table 2. Eleven admitted patients were coinfected with HIV.

Multidrug-resistant 0rganisms

Of the 130 patients tested, 31% (n=40) had one or more MDRO cultured, in total 52 MDROs. ESBL expressing *E. coli* (n=20) was the most common MDRO. Additionally four *K. pneumoniae* and one *M. morganii* and one *E. cloacae* were found ESBL positive. Thirteen from the 26 ESBL positive Enterobacteriaceae were resistant to fluoroquinolones and at least one of the aminoglycosides (both tobramycin and gentamicin were tested). Genes encoding for CTX-M-1-like, CTX-M-15-like, and CTX-M-9 group ESBLs were detected in 13 (50%), 6 (23%), and 5 (19%) isolates, respectively. SHV 238S/240K was detected in one isolate. In one isolate with ESBL phenotype no resistance genes were detected by DNA array. Sixteen Enterobacteriaceae (mainly *E. coli*) were resistant to aminoglycosides and fluoroquinolones without ESBL. One *E. coli* isolate was resistant to colistin. No carbapenemase-producing Enterobacteriaceae were found. With respect to gram positive MDROs, only ten patients were found to carry MRSA.

MDRO carriage appeared to be higher among people from Syria than from Eritrea (7/13 vs 14/64, RR 2.46 (95% CI: 1.24 – 4.88)). Carriage of an MDRO was significantly associated with a shorter duration of stay in the Netherlands: median days in the Netherlands of those with MDRO was 26 (IQR: 4-87) days versus those without MDRO 85 (IQR: 27-316) days, P<0.001. No MDRO was cultured in asylum seekers' babies born in the Netherlands (n=9).

TABLE 2. Purpose of visit; infectious and non-infectious diseases

	Number (%)
Infectious diseases	
Bacterial; pulmonary tuberculosis (n= 44), suspected tuberculosis (n=9) intestinal tuberculosis (n=1), tuberculous peritonitis (n=1), relapsing fever *Borrelia recurrentis* (n=2)	57 (43.8)
Parasitic; malaria (*P. vivax* n=28, *P. falciparum* n=2), leishmaniasis (n=1), schistosomiasis (n=2), (scabies n=7)	40 (30.8)
Clinical presentation of an infection, not otherwise specified; fever, diarrhoea, abscess, respiratory infection, perinatal infection, deep infection of the finger, viral infection, tonsillitis, gastroenteritis, pharyngitis, eosinophilia	17 (13.1)
Viral; viral bronchiolitis (n=2), viral respiratory infection (n=1), hepatitis C (n=9), cytomegalovirus (n=1), disseminated Varicella Zoster Virus infection (n=2)	15 (11.5)
Fungus; nasopharyngeal candida	1 (0.8)
Total	**130 (100)**
Non infectious diseases	
pregnancy, childbirth and the puerperium	40 (21.5)
injury, poisoning and certain other consequences of external causes	23 (12.4)
diseases of the circulatory system	22 (11.8)
certain conditions originating the perinatal period	19 (10.2)
genitourinary system	14 (7.5)
diseases of the nervous system	12 (6.4)
endocrine, nutritional and metabolic diseases	9 (4.8)
external causes of morbidity and mortality	8 (4.3)
diseases of the musculoskeletal system and connective tissue	5 (2.7)
diseases of the digestive system	5 (2.7)
diseases of the blood and immune system	5 (2.7)
diseases of the eye and adnexa	4 (2.1)
diseases of the ear and mastoid process	4 (2.1)
congenital malformations, deformations and chromosomal abnormalities	4 (2.1)
Neoplasms	4 (2.1)
mental and behavioural disorders	4 (2.1)
diseases of the respiratory system	3 (1.6)
diseases of the skin and subcutaneous tissue	3 (1.6)
Total	**186 (100.0)**

DISCUSSION

Around half of the asylum seekers admitted at our university hospital presented with an infectious condition. The carriage rate of MDRO in asylum seekers was 31%. Carriage rate varied by the patients' country of origin and the duration of stay in the Netherlands, however, no CPE was detected.

Given the number of asylum seekers presenting at the national registration centre in Ter Apel, up to 800 daily, the number of admitted patients or patients referred to the emergency department at our university medical centre was low considering the likely adverse conditions during transit.

The most common infectious diseases patients presented with in our hospital were tuberculosis and *P. vivax* malaria. An increase in *P. vivax* malaria in newly arrived Eritrean asylum seekers has been noticed before in Sweden and Norway and its increase seems related to the migration route[19].

The high number of tuberculosis patients in our study results both from a higher incidence in many countries of origin, from the screening by X-ray at arrival in the national reception centre in Ter Apel, and from the asylum seekers with tuberculosis referred by other hospitals in the Netherlands to the UMCG tuberculosis centre. Patients also presented with diseases that are less common such as leishmaniasis or even more seldomly diagnosed in Europe such as the LBRF. After the two patients who reported to our hospital with LBRF[20] additional patients were reported in Switzerland[21] and Germany[22]. Because of the short incubation period the infection is likely to present quickly after arrival and thus at hospitals near to the single national registration centre.

Knowledge about infectious diseases and carriage of MDRO's in asylum seekers is urgently needed to provide adequate care and to enable optimal hospital hygiene strategies. The carriage of MDRO in asylum seekers is high when compared to the Dutch population and also correlates to the carriage rate in country of origin as expected. Asylum seekers have a carriage rate of resistant Enterobacteriaceae comparable to Dutch inhabitants travelling abroad who are similarly known to import multidrug-resistant pathogens. Travellers from the Netherlands showed a high carriage rate of 30.5% of extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-E) after their return from Asia, Africa or South America[23]. It should be considered whether screening policies should not only focus on asylum seekers, but also to consider screening Dutch patients admitted after

international travels to Asia, Africa or South America as well. As an important fact, no CPE was found in asylum seekers. This is different to expectation, as regions of surrounding the country of origin of the asylum seekers are reported to have high prevalence of CPE[24]. As the prevalence of CPE is rising in other European countries, especially in South Europe, but also Germany, asylum seekers that have been treated in hospitals in those countries might get colonized during their travel to the Netherlands. Screening activities needs to be enhanced in order to identify CPE-carriers early. A recent study from Germany showed CPE-carriers and found a multidrug-resistant Gram-negative bacteria carriage rate of almost 61%[25] which is much higher than the MDRO carriage rate in our study. A higher background rate of MDRO in Germany, differences in travel routes and origin of asylum seekers and morbidity on admission, may all have contributed to the difference in MDRO carriage rate.

The aim of this study was to identify and list infectious diseases and carriage of high-risk potential pathogens that may have consequences for public health and infection control. We did not describe details of the non-communicable diseases asylum seekers presented with even though we realize that treatment of these non-communicable diseases are challenging considering the need of optimal compliance and follow-up[26].

The selection of asylum seekers in our hospital based on the insurance number is practical and ensures a complete selection of study participants. Selection based on information in the medical files is likely to be incomplete and selection based on the patients' address leads to exclusion of asylum seekers do not live in the asylum centres or who have been transferred to other centres. The geographical location close to the single national registration centre ensures a true reflection of infectious diseases entering the Netherlands, especially considering the short incubation period from some of the infectious diseases.

Only the diagnoses at admissions were included because of their immediate importance for hospital hygiene measures. Purpose of visits to the out-patient clinic was not reported in this study. Psychiatric disorders are common in asylum seekers[27]. In our study, only four patients were admitted due to psychiatric disorders. However, most likely this low number does not reflect the actual prevalence; most frequently, in the Netherlands, these patients are referred to specialised regional units for transcultural psychiatry.

Another limitation to the study is the percentage of asylum seekers screened at admission. Screening of admitted asylum seekers or asylum seekers presenting at the emergency department was only partially implemented and as a result screening was only done in 48% of the patients. Additional screenings is needed to identify the risk factors for carriage of MDRO strains. These additional screenings will also provide more details on the antimicrobial resistance. Further typing of the MDRO may provide information on the likely route of transmission.

In conclusion, asylum seekers frequently present with infectious diseases, of which many have consequences for infection control. Hospital staff should be prepared to recognize uncommon, poverty-related infectious diseases, especially in hospitals seeing patients who have recently arrived in the Netherlands. A close collaboration with the municipal health centres and the general practitioners at the asylum centres enables a rapid response to new events. Screening for MDRO at admission is necessary at least for originating countries with a high background rate of MDRO to enable the optimal treatment for patients and optimal strategy for infection control.

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03

High prevalence of MRSA and ESBL among asylum seekers in the Netherlands

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ABSTRACT

Migration is one of the risk factors for the spread of multidrug-resistant organisms (MDROs). The increasing influx of migrants challenges local health care systems. To provide evidence for both hospital hygiene measure and empirical antibiotic therapy, we analysed all cultures performed in asylum seekers between January 1st 2014 and December 31st 2015 for methicillin resistant *Staphylococcus aureus* (MRSA) and for multidrug-resistant Enterobacteriaceae (MDRE). We compared these with cultures from the Dutch patient population with risk factors for carriage of MDRO. A total of 7181 patients were screened for MRSA. 7357 *S. aureus* were isolated in clinical cultures. Of 898 screened asylum seekers, almost 10% were MRSA positive. Of 118 asylum seekers with *S. aureus* in clinical cultures almost 19% were MRSA positive. The general patient population had a 1.3% rate of MRSA in *S. aureus* isolates. A higher rate of Panton-Valentine leukocidin (PVL) positive strains (RR: 2.4; 95% CI: 1.6-3.4) was found in asylum seekers compared to the general patient population. In 33475 patients one or more Enterobacteriaceae were obtained. More than 21% of the asylum seekers were carrier of MDRE, most of them producing extended spectrum beta-lactamases (20.3%). 5.1% of the general patient population was MDRE carrier. It can be concluded that asylum seekers present with higher rate of MDRO compared to the general patient population. These results justify continued screening of asylum seekers to anticipate multidrug-resistant organisms during hospital care of patients.

INTRODUCTION

The Netherlands has a low prevalence of multidrug-resistant organisms (MDROs) compared to other countries in Europe. For example, the proportion of invasive methicillin resistant *Staphylococcus aureus* (MRSA) isolates in the Netherlands is less than 1% compared to more than 10% in surrounding countries like Belgium and Germany. Rates up to 37-56% are found in Greece, Portugal and Romania in 2014[1].

To prevent transmission of MRSA, the Netherlands uses a "search and destroy" policy[2]. This policy includes screening of patients from high risk groups, strict isolation at admission of patients suspected to be colonized with MRSA until cultures are shown to be negative, but also eradication treatment of MRSA[3–5]. This strategy was proven to be cost-effective and results in less death due to a bacteraemia[6].

High risk groups include patients who were admitted to hospitals in foreign countries within the last two months. However, optimal screening policy for travellers and asylum seekers is unclear. International travel is considered as a risk factor for acquisition of MDROs like extended spectrum beta-lactamases (ESBL) or carbapenemase-producing Enterobacteriaceae (CPE)[7]. We reported a 31% carriage rate of multidrug-resistant microorganisms, with ESBL-expressing *Escherichia coli* being the most common in asylum seeker patients admitted in a tertiary care University hospital in The Netherlands[8]. However, only a limited number of asylum seekers were screened and these patients may not have been representative for the total asylum seekers' population.

Asylum seekers arriving in The Netherlands originate mainly from Syria, Iraq, Afghanistan and Eritrea[9]. These countries are assumed to have a higher carriage rate of MDRO[10,11]. Due to the sudden high influx of asylum seekers and their expected higher carriage rate of MDRO, Dutch hospitals adopted various screening policies for MDRO in asylum seekers. A national screening policy is not available yet. More knowledge on MDRO carriage is needed to support decision making in national policies on hospital hygiene measures and empirical antibiotic therapy.

In this article, we will describe the rate of MRSA and multidrug-resistant Enterobacteriaceae (MDRE) among asylum seeker patients compared to the general patient population, based upon clinical and screening samples. This information may help to provide the best treatment and screening strategy for asylum seekers.

MATERIALS AND METHODS

The asylum procedure and medical care for asylum seekers

Due to the centralised system of asylum application that is operated by the Netherlands, almost all asylum seekers have to report their arrival at the national reception centre in the north-eastern province of Groningen. A minority reports at the national airport Schiphol. In the national registration centre, asylum seekers are registered and screened for active pulmonary tuberculosis by an X-ray. If (acute) medical care is needed, the patient is treated by the general practitioner at the national registration centre. If more specialised care is needed, the patient is referred to one of the regional hospitals.

The Certe laboratory

The Certe laboratory performs microbiological diagnostics for both general (primary) and specialised (hospital based) health care for a catchment population of about one million inhabitants in the north-east of the Netherlands. Since asylum seekers start their asylum procedure at the central organ for accommodating asylum seekers (COA) in this part of the Netherlands, the majority of samples taken in clinical care from asylum seekers who recently arrived in the country are sent to the Certe laboratory. For both asylum seekers and the general patient population about two third of all diagnostic samples come from one of the nine hospitals in the region. The remainder comes from primary care practitioners. Therefore, samples ranging from first to tertiary care are included.

Selection of participants

A retrospective analysis was performed at the Certe laboratory. The study period and study population were defined by all routine cultures processed between January 1st 2014 and December 31st 2015.

Asylum seekers (and their offspring) were identified by their address if they were living in one of the asylum centres (COAs) in the region. A few asylum seekers living outside the COA were identified because the culture request was done by the physician at the COA health centre. All other patients in the laboratory database were categorised as the “general patient population”.

Much care was taken to clear double entries of asylum seekers from the database. Duplication had occurred in around 3% of cases due to different spellings of names and (rarely) a wrong date of birth. In the general patient population, duplication

is prevented by a citizen service number which is unique for all citizens in the Netherlands. It should be noted that the general patient population in this study includes immigrants, temporary residents from abroad and ex-asylum seekers after receiving their residence permit.

This study was evaluated by the ethics committee and was waived in accordance with Dutch legislation owing to its retrospective nature (University Medical Centre Groningen, METc number 2016/516). No written informed consent was obtained from patients for the use of retrospective data but patient information was anonymized and de-identified prior to analysis.

Methicillin Resistant Staphyloccus Aureus

MRSA was detected both actively and passively. Screening of patients for MRSA carriage can be regarded as an active method of detection whereas passive detection occurs in *S. aureus* isolates from clinical cultures performed to diagnose possible infection.

Screening was not done routinely in all asylum seekers, but most hospitals in the region adopted a screening regimen starting from April 2014. MRSA screening included a nasal, throat, perineum and only in some occasions skin culture. Most asylum seekers were screened in case of (anticipated) admission to the hospital. Additionally to screening, all *S. aureus* isolated from clinical cultures were included in the analyses to study the difference in MRSA prevalence between asylum seeker patients and the general patient population.

Culture swabs collected from patients were transported in clear Amies media and all processed within one day after collection. Clinical cultures were incubated on two to six non-selective media, depending upon possible infectious agents, always including staphylococci and enterobacteriaceae. For screening cultures we used selective media. In case of MRSA screening we incubated a blood agar (Mediaproducts BV) for growth control, a selective Chrom ID MRSA (bioMérieux) and a Mueller Hinton broth with NaCl 2.5% (Mediaproducts BV). The selective broth was subcultured on solid media after one night incubation. Growth of *S. aureus* was confirmed by Staphaurex Plus (Oxoid), coagulase-test and Martineau gene PCR.

Antibiotic susceptibility of *S. aureus* was tested with the Vitek 2 automated system (bioMérieux). Isolates were additionally screened for beta-lactam resistance using the cefoxitin disk diffusion test[12] and MRSA confirmation was completed by detecting the *MecA* or *MecC* gene by PCR.

Of MRSA isolates the presence of the Panton-Valentine leukocidin (PVL) gene was tested with PCR. The PVL cytotoxin is associated with increased virulence of *S. aureus*. It is particularly associated with skin and soft tissue infections[13]. Molecular typing of MRSA isolates was done using Multiple Loci Variable Number Tandem Repeat Analysis (MLVA) performed by the Netherlands National Institute for Public Health and the Environment, which functions as the Dutch national reference centre for MRSA. The Multilocus sequence typing (MLST) clonal complex can be derived from most MLVA types.

Multidrug-resistant Enterobacteriaceae

Similarly as for MRSA, MDRE can be detected both actively and passively. All Enterobacteriaceae isolated from clinical cultures were selected. As for MRSA routine MDRE screening of asylum seekers, started only halfway the study period. MDRE screening was performed using rectal swabs, which were processed within one day after collection. A growth control on blood agar and three selective solid media, a McConkey with ciprofloxacin 0,5 mg/l and gentamicin 2 mg/l (Mediaproducts BV), a ChromID ESBL and a ChromID Carbapenemase agar (both bioMérieux) were incubated.

Three patterns of MDRE were distinguished: Extended Spectrum Beta-Lactamase (ESBL), Fluoroquinolone plus Aminoglycoside Resistant Enterobacteriaceae (QARE) and carbapenemase-producing Enterobacteriaceae (CPE). Suspicious colonies were identified on species level by using MALDI-TOF. Only after a correct and plausible identification, the antibiotic susceptibility of Enterobacteriaceae was tested with the Vitek 2 system.

The antibiotic susceptibility of Enterobacteriaceae was tested with the Vitek 2 system. Presence of ESBL was confirmed with cefotaxime-clavulanate, ceftazidime-clavulanate and cefepime-clavulanate E tests (bioMérieux)[14]. Possible CPE was confirmed by PCR (Check-Points, Check-MDR CT102).

Statistical analysis

Data were collected and analysed using Microsoft Excel and SPSS (version 2.22). Differences in proportions were tested for significance by Pearson's uncorrected chi-squared test or the Fisher's exact test as appropriate. Relative risk ratios (95% CI) were calculated for the virulence factor PVL and the MDRO rate.

RESULTS

In total 1071 asylum seekers were included in the study of which 973 had MRSA screening cultures or *S.aureus* in one or more clinical cultures and 859 had MDRE screening cultures or at least one of the enterobacteriaceae in clinical cultures. Of these 1071 asylum seekers 545 had cultures submitted to the laboratory by a primary care worker and 627 had cultures done by the second line (hospital) care.

Methicillin Resistant Staphylococcus Aureus

During the study period 898 asylum seekers were actively screened for MRSA with a total of 3,106 cultures. Of these patients 87 (9.7%) were found to carry MRSA. In these patients MRSA was most often detected in their throat cultures (53; 61%), followed by nasal cultures (50; 57%) and perineum cultures (43; 49%).

In the same period 133 clinical cultures of 118 asylum seekers were positive with *S. aureus* isolates. Of these patients 22 (18.6%) carried MRSA (Table 1). 30.3% of the clinical isolates was a pus sample. No MRSA was obtained from blood cultures.

Of the general patient population 66 individuals were excluded from analyses because they had been identified with MRSA before 2014. Screening for MRSA in the general patient population was mainly done in persons at increased risk of MRSA carriage or in case of a contact investigation. In brief, patients considered to have an increased risk are patients working with livestock and patients who have been admitted to a foreign hospital over the last 2 months. More detailed information on risk factors for which screening on MDRO is performed in the Netherlands can be found in the national guidelines[3].

By screening, 177 new MRSA carriers were found in patients from the general patient population. A lower number of MRSA was found in patients with infections; in the clinical cultures from the general patient population only 92 new patients with MRSA were found (Table 1).

Both screening and clinical cultures of asylum seekers were significantly more often MRSA positive than of the general patient population ($p < 0.001$).

Each unexpected finding of MRSA in a clinical culture of an admitted patient was followed by screening of all contacts of this patient (including both caretakers and patients). Hospital acquired MRSA was defined as MRSA found in case of contact tracing around an index patient and if both index and contact strains were similar.

According to that definition 25 of the 269 (9%) MRSA positive general patient (or caretaker) population had a hospital acquired MRSA, compared to one (1%) of the MRSA positive asylum seekers' population.

TABLE 1. Results of MRSA screening and MRSA among *S. aureus* isolates cultured from clinical samples, during 2014 – 2015, at the Certe laboratory.

	Number of patients	Number with MRSA	% with MRSA
MRSA screening			
General patient population*	6283	177	2.8%
Asylum seekers	898	87	9.7%
***S. aureus* in clinical samples**			
General patient population	7239	92	1.3%
Asylum seekers	118	22	18.6%
total from screening and clinical samples**			
General patient population	12989	269	2.1%
Asylum seekers	973	100	10.3%

** screened at hospital admission because of increased risk of MRSA carriage or contact investigation*
*** 533 of the general patient population and 43 asylum seekers had both screening and clinical cultures (number of totals less than sum of screening and clinical samples).*

MRSA genotyping

MRSA strains of asylum seekers were significantly more often PVL positive (42.0%) than of the general patient population (17.8% (RR: 2.4; 95% CI:1.6-3.4)). A high proportion (47.2%) of MRSA in the general patient population was livestock associated: CC398 or MLVA complex MC2236. This type of MRSA was never PVL positive. None of the asylum seekers had a livestock associated MRSA. After excluding livestock associated MRSA, 33.8% of the remaining general population patients' MRSA was PVL positive, still lower than the proportion of PVL in asylum seekers' MRSA, but this difference is not statistically significant ($p = 0.19$).

CC398 was by far the most common type of MRSA among the general patient population. In asylum seekers MRSA CC1 was the most prevalent type and 18 (66.7%) of these strains were PVL positive. CC5, CC8 and CC22 were isolated in both patient categories, but CC22 significantly more often in asylum seekers ($p < 0.001$). CC8 was evenly distributed in both groups, but remarkably none of the

asylum seeker strains was PVL positive, whereas 25 (92.6%) of the general patient population strains were PVL positive. MLVA complex MC0281 (related to CC88) was often found among asylum seekers. Of these strains 9 (60%) were PVL positive.

TABLE 2. Genetic characteristics of MRSA isolates of the general versus the asylum seeker patient population.

	General patient population	Asylum seekers	Total
Number of new MRSA*	269	100	369
Livestock associated MRSA	127 (47.2%)	0	127 (32.0%)
PVL** positive MRSA	48 (17.8%)	42 (42.0%)	90 (24.4%)

Most prevalent MLST complexes***	Number (%)	PVL-positive (%)	Number (%)	PVL-positive (%)	Number (%)	PVL-positive (%)
CC398	124 (46.1)	0 (0.0)	0 (0.0)	0 (0.0)	124 (33.6)	0 (0.0)
CC5	46 (17.1)	3 (6.5)	5 (5.0)	0 (0.0)	51 (13.8)	3 (5.9)
CC8	27 (10.0)	25 (92.6)	7 (7.0)	0 (0.0)	34 (9.2)	25 (73.5)
CC22	12 (4.5)	0 (0.0)	20 (20.0)	0 (0.0)	32 (8.6)	0 (0.0)
CC30	11 (4.1)	10 (90.1)	3 (3.0)	2 (66.7)	14 (3.8)	12 (85.7)
CC45	11 (4.1)	0 (0.0)	0 (0.0)	0 (0.0)	11 (2.9)	0 (0.0)
CC1	2 (0.7)	1 (50.0)	27 (27.0)	18 (66.7)	29 (7.9)	19 (65.5)
CC88	2 (0.7)	2 (100.0)	15 (15.0)	9 (60.0)	17 (4.6)	11 (64.7)
CC80	6 (2.2)	6 (100.0)	5 (5.0)	5 (100.0)	11 (3.0)	11 (100)

Multidrug-resistant Enterobacteriaceae

For this part of the study we included 58,748 Enterobacteriaceae isolated from clinical cultures. Of these, 215 isolates were obtained from asylum seekers and 58,533 from the general patient population. Among asylum seekers 38 (17.7%) of their isolates were MDRE versus 2,554 (4.3%) of isolates from general population patients. 78.1% of the clinical isolates was obtained from urine samples.

Screening was mostly done in patients who had previously been colonized with MDRE or after admission in a foreign hospital. Differently than for MRSA, no contact tracing was done in case of MDRE. In total, sensitivity testing was performed on 5,300 isolates from screening cultures. Among those 1,557 (29.4%) were MDRE.

Details of MDRE carriage detected by screening or in clinical cultures are given in Table 3. Most MDRE were of the ESBL type. Many strains carried more than one resistance pattern.

TABLE 3. Number of patients tested and proportions of multidrug-resistant Enterobacteriaceae (MDRE) in screening and clinical cultures, during 2014 – 2015, at the Certe laboratory.

	Number of patients	% MDRE	% ESBL	% QARE	% CPE
MDRE screening					
General patient population*	1763	24.4%	16.3%	12.5%	0.06%
Asylum seekers	751	21.0%	20.0%	4.4%	0.1%
Relative Risk (95% CI)		0.9 (0.7-1.0)	1.2 (1.0-1.5)	0.4 (0.2-0.5)	2.4 (0.1-85.6)
Enterobacteriaceae in clinical samples					
General patient population	31,798	4.6%	2.7%	2.6%	0.02%
Asylum seekers	150	21.3%	19.3%	7.3%	0.0%
Relative Risk (95% CI)		4.6 (3.3-6.3)	7.2 (5.0-10.0)	2.8 (1.5-5.1)	0.0 (0-196.5)
totals from screening and clinical samples**					
General patient population	32,616	5.1%	3.2%	2.8%	0.02%
Asylum seekers	859	21.4%	20.3%	4.9%	0.1%
Relative Risk (95% CI)		4.2 (3.7-4.8)	6.3 (5.5-7.3)	1.75 (1.3-2.4)	6.33 (0.3-52.4))

** screened at hospital admission because of increased risk of MDRE carriage*
*** 945 of the general patient population and 42 asylum seekers had both screening and clinical cultures (number of totals less than sum of screening and clinical samples)*

CPE were rarely found. Among asylum seekers no clinical culture contained CPE and only one patient had a CPE *E. coli* in his screening culture.

Table 3 shows a striking difference in MDRE rates in asylum seekers compared to the general patient population (21.4% vs. 5.1%). This difference mainly results from the clinical samples. A relatively small number of the general patient population was screened for MDRE because of specific risk factors. In these patients the carriage rate of MDRE is similar to the rate in asylum seekers, except for carriage of the QARE type resistance, which was less common in asylum seekers ($p < 0.001$).

In clinical cultures MDRE, ESBL and QARE were all significantly more prevalent among asylum seekers than general population patients ($p < 0.001$).

DISCUSSION

The aim of this retrospective study was to assess carriage rates of MRSA and multidrug-resistant Enterobacteriaceae (MDRE) among asylum seekers and to compare these to the general patient population. The data we used is unique because of the large number of patients from primary till tertiary care and included both screening and clinical cultures. For this reason, the results can be expected to represent the overall asylum seekers' population arriving in the Netherlands during the study period. Knowledge on MDRO carriage is needed to provide evidence for both hospital hygiene measures and empirical antibiotic therapy.

Particularly higher carriage rates of MRSA were found in the asylum seekers' population than in the Dutch patient population with risk factors for MDRO carriage. Among asylum seekers less MRSA was found by screening than in clinical cultures, suggesting that these MRSA are either more pathogenic or these infections were not responding to treatment and therefore more likely to be cultured than infections caused by beta-lactam sensitive *S. aureus*. The higher pathogenicity of the MRSA is supported by PVL rates which were twice as high in MRSA from clinical cultures as in strains obtained by screening. The MRSA prevalence of the general population may be better reflected by clinical cultures than screening cultures, because the latter was only done in a small subset of either high risk or contact patients.

Higher MRSA and MDRE carriage rates in asylum seekers were described before[15,16] as was the presence of PVL in asylum seeker strains[17,18]. Reinheimer et al[15] detected a 61% MDRO rate in refugee patients admitted to a University Hospital. This is much higher than the rate found in our study and could be explained by a difference in study population. This tertiary care patient category may have higher MDRO rates than those requiring first or second line care. Samples from different primary health centres and hospitals reflect both first, second and tertiary care. This increases the external validity of our study results since it is expected to reflect asylum seekers with different health care needs.

Based on epidemiological data, hospital acquired MRSA was more common in the general patient population than in the asylum seeker population. The lack of data on medical history including hospital admissions could have led to an underestimation of hospital acquired MRSA in the asylum seekers.

High MRSA rates in the asylum seekers' population may be due to a high prevalence in their homelands and thus reflect long-term stable carriage, or they can be due to transmission between asylum seekers. The finding that among 104 asylum strains 56 different MLVA types were found, argues for the first hypothesis. Only two MLVA types were isolated more than ten times. One of these types, MT0281, belonging to MC0281 (CC88) was found in 12 strains, half of which were PVL positive. MT4594, belonging to MC0001 (CC1), was found 11 times of which all strains were PVL positive. More information on the MC-types in the country of origin is needed to interpret the variety of MC-types carried by asylum seekers.

The asylum seekers' population carriage rates of MDRE were higher than the carriage rate in the general patient population. As only a small number of high risk general population was screened for MDRE, the most valid comparison between the two study groups can be done with MDRE rates found in clinical cultures. Asylum seekers have 4 to 5 time higher rates of MDRE than the general population and particularly more ESBL. International travel is described as a risk factor for the colonization of multidrug-resistant organisms in travellers[19,20]. and a higher carriage rate of ESBL was also described in refugee minors arriving in Germany. However, this study group is only represented by refugee minors under 18 years old and may not represent the overall population[21]. Interestingly, differences in QARE rates are only small in our study. CPE was rare in both groups, but monitoring is necessary since the carriage rate of CPE may vary if the population of asylum seekers changes and includes e.g. more patients with chronic diseases and earlier hospitalizations.

Reasons for higher MDRE carriage in asylum seekers may be similar as for MRSA carriage. As MDRE is more diverse and we know less from typing of these organisms we cannot speculate about the origin of these organisms.

The method used for MDRO screening is sensitive and efficient. However, a limitation of this method is that MDRO may be missed if they colonized a different body site than the regular ones. Another limitation is that MDRO found by screening may only represent temporary carriage and may have little or none clinical relevance. Still people with MDRO are registered and health-care workers are alerted whenever they take care of an MDRO carrier.

The total carriage rate of MRSA in the Dutch patient population with risk factors exceeds the prevalence observed in the overall Dutch population (<1%). The screening was performed in a small subset with risk factors of MRSA carriage like working with livestock or close contact with known MRSA carrier. Similarly

the patients selected for MDRE screening had risk factors like foreign hospital admissions, earlier positive screening results. The prevalence of the general patient population may be better reflected by clinical cultures than screening cultures.

In asylum seekers there was no difference between MDRE in screening and clinical cultures, suggesting that both are a good reflection of MDRE rates in the asylum seeker patient population. This provides evidence for screening for MDRE in asylum seekers arriving in the Netherlands. Carriage of ESBL may be a threat especially for children since treatment options for children are limited[22]. The current study is performed in the Netherlands where ESBL carriage is still considered a reason to screen and isolate patients. The study group represents the Dutch asylum seekers' population but consists of a heterogeneous group of people originating from many countries with different travel routes and possible hospital admissions before arriving in the Netherlands. To customize the Dutch screening policy additional information on these risk factors is needed.

Compared to asylum seekers the general patient population had more clinical than screening cultures, particularly with Enterobacteriaceae. Only a minority of the Dutch patient population with risk factors is screened for MDRE, namely those at high risk of resistance. That explains the much higher yield of MDRE from screening than clinical cultures.

In conclusion, our study shows significantly higher rates of MRSA and MDRE among the asylum seekers' population than the general patient population. These differences justify screening of the asylum seekers' population at admission in the hospital as these organisms may be a threat to the patient and transmission in the hospital should be prevented.

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04

Proportion of asylum seekers carrying multidrug-resistant organisms is persistently increased after arrival in the Netherlands

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ABSTRACT

Background

Several studies have shown a high prevalence of multidrug-resistant organisms (MDROs) amongst asylum seekers when compared to the general population. The aim of this study is to assess the duration of MDRO carriage in this population.

Materials and Methods

Data were retrospectively collected between January 1st 2014 through December 31st 2016. Study material included screening samples for MDRO carriage and clinical samples from asylum seekers in need of medical care. The study focused on methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant Enterobacteriaceae (MDRE). The rates of MRSA and MDRE detected were calculated every four weeks after arrival in the Netherlands.

Results

Samples from 2091 asylum seekers were included. 1270 (60.7%) were female, median age was 26 years (IQR 20–34) and median number of days in the Netherlands until first sample was 67 (IQR 4–235). In the patients' first obtained samples, the rate of MRSA varied between 4.5 and 13.0% per time interval after arrival. The rate of MDRE fluctuated between 7.4% and 25.0%. No particular decline in positivity rates in first obtained samples was observed after arrival in the Netherlands. In the group of asylum seekers who arrived more than one year ago, MRSA was isolated in a percentage of 5.1% ($n = 273$, median months after arrival 34.1 (IQR 16.5–63.1)) and MDRE in 9.4% ($n = 276$, median months after arrival 35.4 (IQR 17–65)).

Conclusion

To our knowledge, this is the first study demonstrating that carriage rate of MDRO in asylum seekers remains high even after prolonged stay in the Netherlands. Longitudinal data on MDRO carriage after arrival in countries with a low MDRO prevalence are needed to determine optimal screening strategies, infection control measures and empirical antibiotic therapy.

BACKGROUND

During the last decade, millions of refugees have entered European grounds as a result of warfare, violence, political instability and poverty in several Asian, African and Middle Eastern areas. Furthermore, ongoing civil wars in Syria and Afghanistan have led to an unprecedented influx of refuge seekers in Europe [1]. Several studies have been conducted on carriage of multidrug-resistant organisms (MDROs) in asylum seekers. A recently published systematic review and meta-analysis on antimicrobial resistance amongst migrants in Europe, showed a pooled prevalence of any detected antimicrobial resistance (AMR) carriage or infection of 25.4% (95% CI 19.1–31.8). The pooled prevalence of methicillin-resistant *Staphylococcus aureus (*MRSA) was 7.8% (95% CI 4.8–10.7), and of multidrug-resistant Gram negative bacteria (MDRGN) 27.2% (95% CI 17.6–36.8[2].

The high proportion of MDRO carriage among asylum seekers may have implications for countries with low MDRO prevalence like the Netherlands. Previously studied MDRO carriage rate amongst asylum seekers in need of medical care in the Netherlands was compared to the MDRO rate in the Dutch hospitalized population. A prevalence of 21.4% compared to 5.1% for multidrug-resistant Enterobacteriaceae (MDRE) and 9.7% versus 1.3% for MRSA in the asylum seekers population and the Dutch population was found, respectively. These findings support a policy of MDRO screening amongst asylum seekers in the Dutch setting[3].

The current Dutch protocol recommends screening of all asylum seekers for MRSA and MDRGN carriage at hospital admission or emergency care visit, regardless of other risk factors[4,5]. The protocol does not provide information on the needs of screening in relation to the time that elapsed since arrival into the country. Information on duration of MDRO carriage is available for travelers. In a Dutch study, 83.2% of travelers who tested positive for MDRGN after visiting high prevalence countries, were spontaneously decolonized within 6 months after returning to the Netherlands[6]. The same pattern was observed in a German study in which 91.4% of returning travelers who tested positive for Extended Spectrum Beta-Lactamase(ESBL), were decolonized after 6 months[7]. Rational screening for MDRO in asylum seekers in the Netherlands can be improved based on information on the duration of MDRO carriage in asylum seekers after arrival in the Netherlands and can be more targeted based on risk factors for MDRO carriage within the group of asylum seekers.

In this retrospective study, we examine MDRO carriage among asylum seekers focusing on the time that elapsed since arrival in the Netherlands.

MATERIALS AND METHODS

Asylum seeker procedure in the Netherlands and the Certe laboratory

Almost all asylum seekers arriving in the Netherlands start their asylum procedure at the national reception center for asylum seekers in the north-eastern part of the Netherlands. Asylum seekers who are in need of (direct) medical care will report at the health care services in the asylum seeker center. The general practitioner of the health care services may refer the asylum seeker to a hospital in the area. More information on the asylum seeker procedure in the Netherlands can be found in a previously published paper [3]. The Certe laboratory performed all the routine microbiological diagnostics for this north-eastern part of the Netherlands, including samples from eight hospitals, general practitioners, nursing homes and asylum seeker centers in the region.

Study design

Data was retrospectively collected from the Certe laboratory and the national health care system for asylum seekers. Study material included screening samples for MDRO carriage before admission (throat, rectum, and nose) and clinical samples (e.g. blood, wounds, and urogenital) from asylum seekers. All of these samples were obtained as part of the standard care. EUCAST guidelines were used for susceptibility interpretation[8]. Patients who tested negatively during their first visit at the hospital, were retested on re-admission or when they visited the emergency department. Results from these samples between January 1st 2014 and December 31st 2016, were aggregated. We focused on MRSA, Vancomycin Resistant Enterococci (VRE) and multidrug-resistant Enterobacteriaceae (MDRE). In MDRE three resistance patterns were distinguished: Extended Spectrum Beta-Lactamase (ESBL)-production, Fluoroquinolone plus Aminoglycoside Resistant Enterobacteriaceae (QARE), Carbapenemase-Producing Enterobacteriaceae (CPE)[3].

Selection of participants

All asylum seekers are registered on the asylum seeker center's address. The postal codes referring to these addresses were used to identify patients as asylum seekers for the study. Demographic data such as age, sex, and date of sampling were collected from the laboratory system. Country of origin and arrival date in the

Netherlands was documented using the health care system for asylum seekers. In case the arrival date was missing, the date of first visit to a general practitioner was used.

Bacterial detection and analysis

MRSA

Screening samples were incubated on blood agar (Mediaproducts BV) for growth control, a selective Chrom ID MRSA (bioMérieux) and a Mueller Hinton broth with NaCl 2.5% (Mediaproducts BV). The selective broth was also subcultured on selective Chrom ID MRSA (bioMérieux) after one-night incubation. Growth of *S. aureus* was confirmed by Staphaurex Plus (Oxoid) and coagulase-test[3].

MDRE

The selective agar plates used for MDRE detection were McConkey with ciprofloxacin Carbapenemase agar (both bioMérieux). Presence of ESBL was confirmed with cefotaxime-clavulanate, ceftazidime- clavulanate and cefepime-clavulanate Etest strips (bioMérieux). Possible CPE was confirmed by CIM test and PCR and typed by the national reference network for CPE at the RIVM (National Institute for Public Health)[3].

VRE

For selective culture of Vancomycin Resistant Enterococcus faecalis or Enterococcus faecium (VRE,) rectal swabs were incubated for 2 nights at 35 °C in Brain Heart Infusion broth with 2% NaCl and 16 mg/l gentamicin plus 16 mg/l vancomycin. Subcultures were made on chromID VRE agar plate (bioMérieux). VRE confirmation was done by VanA/ VanB PCR using GeneXpert (Cepheid).

Statistical analysis

Data was analyzed with SPSS Version 23.0. Descriptive statistics were used for the general characteristics and the duration of MDRO carriage. Data is presented as median with 25–75% inter quartile range (IQR) as appropriate. To study the carriage rate of MRSA and MDRE over time, all dates of first samples taken were compared to the arrival date in the Netherlands. Carriage duration through time was analyzed by four-weeks periods. Due to small population size the last period was defined as week 53 and after and is represented as one group. For determining MDRO carriage over time, we excluded all clinical samples, considering no antibiotic usage data were available.

RESULTS

General characteristics

From January 2014 through December 2016, 2091 asylum seekers were tested for MDROs as part of their standard care. Screening and clinical samples were obtained based on the cause of visit/admission to the hospital and the anticipated causative agents leading to different number of asylum seekers tested for MRSA and MDRE. General characteristics of both study groups can be found in Table 1.

TABLE 1. General characteristics of the study population

Number of asylum seekers (n=2091)	
Sex (female (%))	1270 (60.7)
Age in years median (IQR*)	26 (20-34)
Number of days in the Netherlands until first sample (IQR)	67 (4-235)

	Number of asylum seekers	**Number of MDRO positive asylum seekers (%)**
Total number of asylum seekers tested for MRSA analysis	1954	185 (9.5)
Screening analysis	1777	159 (8.9)
Clinical analysis	177	26 (14.7)
Total number of asylum seekers tested for MDRE analysis	1789	331 (18.5)**
Screening analysis	1555	298 (19.2)
Clinical analysis	234	48 (20.5)

***IQR = Interquartile range*

** 15 positive asylum seekers had both for screening and clinical samples*

In total, 1954 asylum seekers were tested for MRSA, of which 185 (9.3%) were positive. Nine hundred seventy two asylum seekers were all tested negative for VRE. Furthermore, 1789 asylum seekers were tested for MDRE of which 331 (18.5%) tested positive. Specifics regarding screening to clinical samples ratio can be found in Table1. MRSA and MDRE were relatively more frequently detected in asylum seekers originating from Iraq (19.1 and 43.2%, respectively) and Syria (15.8 and 39.9%, respectively). An overview of the country of origin of the study group and the number of people tested positive for MDRO within the total group, originating from the same country can be found in Figure 1.

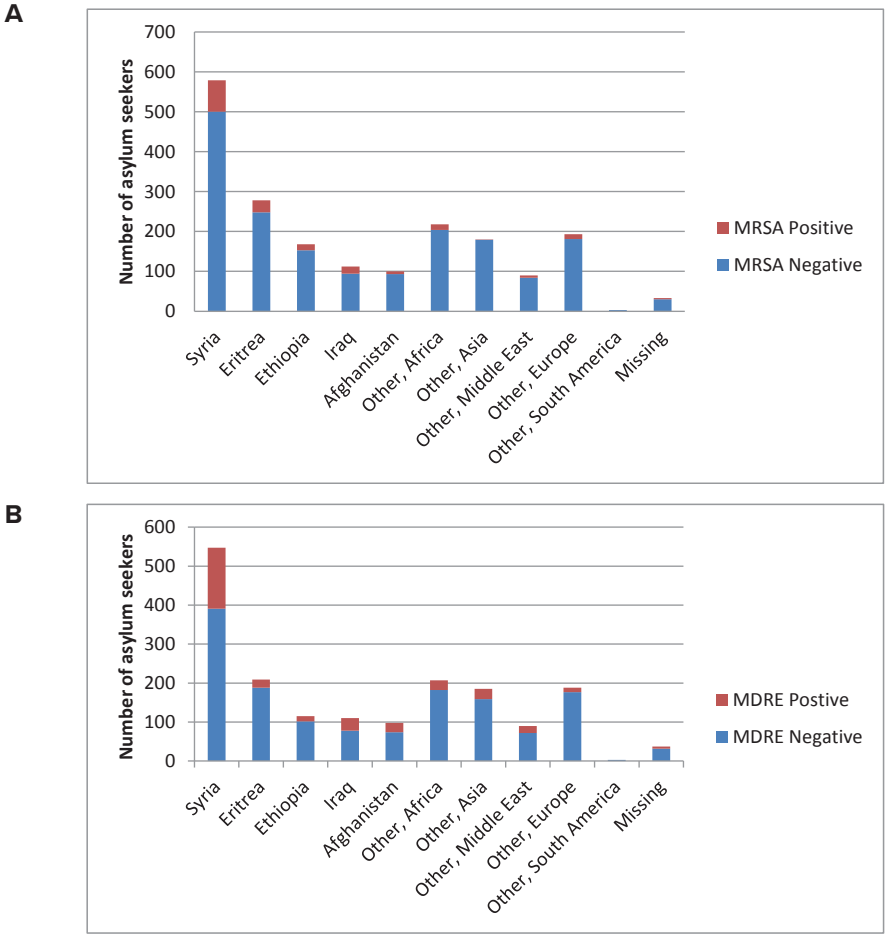


FIGURE 1 A. Number of asylum seekers that tested positive for MRSA compared to the number of asylum seekers that tested negative for MRSA within country of origin. **B.** Number of asylum seekers that tested positive for MDRE compared to the number of asylum seekers that tested negative for MDRE within country of origin

Resistance patterns in MDRE

E. coli was the most frequently detected MDRE species ($n = 301$). The most frequent resistance pattern detected was ESBL-production followed by a combination of ESBL-production and Fluoroquinolone/Aminoglycoside resistance. Of note, one of

the strains co-exhibited all three patterns of resistance. The carrier of this specific strain originated from Syria. Detailed numbers of species with specific resistance patterns can be found in Table 2.

TABLE 2. Number of isolates belonging to different microbial species and the respective resistance patterns they exhibited.

Microbial species	ESBL*	QARE**	ESBL + QARE	CPE*** + ESBL	CPE + ESBL + QARE
Escherichia coli n=301	240	12	48	1	0
Klebsiella pneumonia n=26	19	0	7	0	0
Klebsiella oxytoca	0	0	1	0	1
Proteus mirabilis	5	2	0	0	0
Morganella morganii	0	0	2	0	0
Enterobacter cloacae	3	0	1	0	0
Citrobacter freundi	1	0	0	0	0
Total number of strains (n=343****)	268	14	59	1	1

** ESBL = Extended Spectrum Beta-Lactamase*

*** QARE = Fluoroquinolone plus aminoglycoside resistant Enterobacteriaceae*

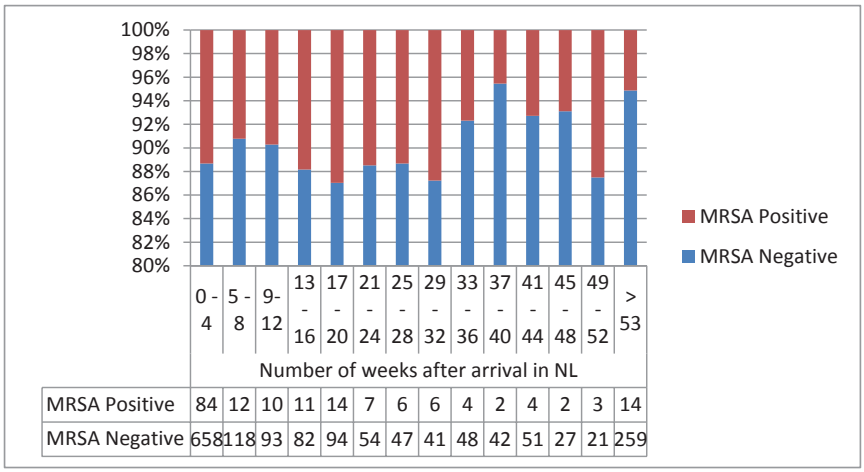
**** CPE = Carbapenemase-Producing Enterobacteriaceae*

*****Total number of isolates (n=343) is higher than the number of positive sample because same samples were positive for more than one MDRE.*

MDRO carriage

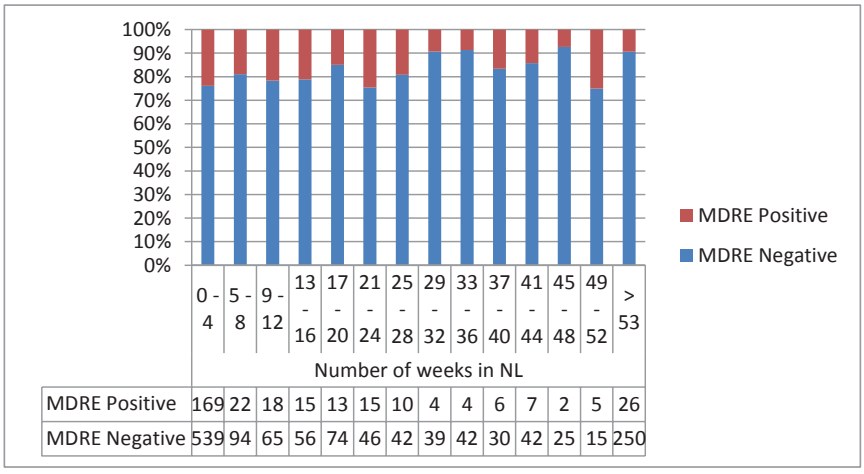
MDRO carriage in the first culture

Figures 2 and 3 show the carriage rate of MRSA and MDRE in asylum seekers in their first obtained sample in percentages over time. For MRSA, the median time after arrival in the last group (over 53 weeks) was 1022 days (IQR 494 -1892) and for MDRE was 1063 days (IQR 510-1950)



	0 - 4	5 - 8	9- 12	13 - 16	17 - 20	21 - 24	25 - 28	29 - 32	33 - 36	37 - 40	41 - 44	45 - 48	49 - 52	> 53
MRSA Positive	84	12	10	11	14	7	6	6	4	2	4	2	3	14
MRSA Negative	658	118	93	82	94	54	47	41	48	42	51	27	21	259

FIGURE 2. Percentage of MRSA in first obtained sample in relation to time (weeks) after arrival in the Netherlands. Repeated samples are excluded



	0 - 4	5 - 8	9 - 12	13 - 16	17 - 20	21 - 24	25 - 28	29 - 32	33 - 36	37 - 40	41 - 44	45 - 48	49 - 52	> 53
MDRE Positive	169	22	18	15	13	15	10	4	4	6	7	2	5	26
MDRE Negative	539	94	65	56	74	46	42	39	42	30	42	25	15	250

FIGURE 3. Percentage of MDRE in first obtained sample in relation to time (weeks) after arrival in the Netherlands. Repeated samples are excluded

MDRO carriage during follow-up

MRSA

Of the 1954 asylum seekers tested for MRSA, follow-up screening samples were performed in 442 of them after a median of 60 days (IQR 27–109) after the first sample was obtained. Forty seven asylum seekers that tested positive for MRSA, were followed up with screening samples. Twenty five of the asylum seekers who tested positive for MRSA in the first obtained sample, tested positive in their follow-up samples which were obtained after a median of 80 days (IQR 20.5–101).

Six of the asylum seekers who tested positive for MRSA in the first obtained sample, tested negative in the subsequent samples which were obtained after a median of 48.5 days (IQR 43.75–147). It is unknown if these patients received eradication or treatment before retesting.

There were 16 asylum seekers who initially tested negative for MRSA but tested positive for MRSA in repeated screening sample obtained after a median 63 days (IQR 8.5–109).

MDRE

Of the 1789 asylum seekers tested for MDRE, follow up screening samples were performed in 365 of them after a median of 57 days (IQR 27–104) after the first sample was obtained. Seventy-one of the asylum seekers who tested positive for MDRE, were followed up with screening samples. Thirty-eight of the asylum seekers who tested positive for MDRE in the first obtained sample, tested positive in their follow-up samples which were obtained after a median of 60.5 (IQR 16.8–99.8).

Twenty nine of the asylum seekers who tested positive for MDRE in the first obtained sample, tested negative in the subsequent samples which were taken after a median of 87 days (IQR 39–179). It is unknown if these patients received treatment before the retesting. There were four asylum seekers who initially tested negative for MDRE but tested positive for MDRE in repeated screening samples taken after a median of 28.5 days (IQR 5–163.8).

DISCUSSION

In this study, a large number of both screening and clinical samples were collected from 2091 asylum seekers. The most frequently isolated resistant microbes were MRSA and ESBL-producing *E. coli*. The percentage of MRSA and MDRE in asylum seekers who tested positive for MRSA and/or MDRE changed over time. However, no clear pattern of decline or increase was observed.

Several studies have described MDRO carriage or outbreaks amongst Syrian refugees. In a Swiss study, 261 refugees were screened for MRSA of which 41 (15.7%) tested positive. Furthermore 240 refugees were screened for ESBL-producing Gram negatives of which 57 (23.7%) tested positive[9]. In addition, studies in Germany have shown MDRO prevalence in asylum seekers ranging between 24.7% and 60.8%. The main resistant strains isolated were MRSA, and ESBL-producing Enterobacteriaceae[10,11]. The wide range of carriage observed among these studies reflects the differences among the study population such as age, country of origin, included samples, e.g. screening and/or clinical, risk factors like previous hospitalization and differences in sampling strategies and laboratory methods. Our findings align with high MDRO range amongst this vulnerable population.

Studies have shown that the duration of MDRO colonization in humans vary across strains – e.g. the median clearance for MRSA varied between 5.9 and 9 months[12,13]. Regarding ESBL-producing Enterobacteriaceae, a median clearance of 6.6 months was observed[14]. In an Australian study, 26 out of 48 (54%) international travelers cleared all resistant *E. coli* within two months after their return, while 18% remained colonized six months post-travel[15]. Furthermore, a study from the Netherlands, a country of low prevalence for MDROs, investigated MDRO carriage rate and its duration over time in travelers returning from high prevalence countries. 113 people who were negative for MDRGN before travelling tested positive after returning to the Netherlands. 83.2% of them were spontaneously decolonized within 6 months after returning to the Netherlands[6].

We therefore expected the MDRO prevalence amongst our population group to decline over time, especially when taking under consideration the low prevalence of MDRO in the Netherlands. However, a significant percentage of our population group tested positive in their first sample taken even after more than one year after arrival in the Netherlands.

Multiple possible explanations for the prolonged duration of carriage of MDROs in this population can be considered. Firstly, a large number of the study group spent most of the study period living together in one of the asylum seeker centers in the northern part of the Netherlands. MDRO carriers could serve as a natural reservoir, forming a cluster of such strains and close contact within the facility could lead to transmission[16]. Secondly, the possibility of MDRO strains being part of the normal flora should be considered. In such cases, the resistant strains colonize the gut microbiome indefinitely and detecting them depends on the screening methods and their microbial load at the time of screening.

Due to the retrospective aspect of this study we did not have access to important information like traveling and antibiotic consumption history. However, our study population exhibited wide ranges regarding age, country of origin, and included both hospitalized and non-hospitalized asylum seekers. No systematic screening upon arrival in the Netherlands, and follow up screening was performed in asylum seekers. Only in asylum seekers in need of medical care multiple times or admitted to the wards, follow up screening was performed.

Antibiotic consumption in general is low in the Netherlands. The antibiotic consumption data by the study population is unknown to us, but a small percentage of the asylum seekers population face health issues such as infections and might have been treated with antibiotics. This could have contributed to emergence of resistant strains and/or prolonged duration of carriage due to antibiotic pressure.

In order to confirm or reject our hypothesis regarding prolonged duration of carriage, the next rational step would be to perform a prospective, longitudinal study of a cohort. However, it is unsure whether it could be perceived as ethical to approach asylum seekers for participation in a prospective trial upon arrival considering their dependent position. Moreover, molecular analysis of the strains and thorough examination of their phylogenetic relatedness could reveal important information on transmission and cluster formation.

Conclusion

In conclusion, our findings verify the high MDRO prevalence among the asylum seeker population. To our knowledge, this is the first study demonstrating that carriage rate of MDRO remained high even after long term stay in the Netherlands. This finding has consequences for the optimal screening strategy, infection control measures and empirical antibiotic therapy. A prospective, longitudinal study of a cohort should be performed to confirm our findings. The dependent position

of asylum seekers should however be carefully considered in the study design. Moreover, molecular analysis of the strains and thorough examination of their phylogenetic relatedness could reveal important information on transmission and cluster formation.

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05

Predominance of CTX-M-15–producing Escherichia coli belonging to MLST ST131 among ESBL isolates from asylum seekers in the Netherlands

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ABSTRACT

Introduction

Numerous studies show increased prevalence of MDR bacteria amongst asylum seekers, but data on the molecular profiles of such strains are limited. We aimed to evaluate the molecular profiles of ESBL-producing *Escherichia coli* (ESBL-*E. coli*) strains isolated from asylum seekers and investigate their phylogenetic relatedness.

Methods

Whole genome sequencing data of ESBL-*E. coli* isolates from asylum seekers, retrieved from 1 January to 31 December 2016, were analysed to assess MLST STs, *fim* types, phylogroups and resistance genes. Fifty-two ESBL-*E. coli* isolates from the Dutch–German border region were used for genome comparison purposes as a control group.

Results

Among 112 ESBL-*E. coli* isolates from asylum seekers, originating mostly from Syria (*n*=40) and Iraq (*n*=15), the majority belonged to ST131 (21.4%) and ST10 (17.0%). The predominant gene for β-lactam resistance was $bla_{\text{CTX-M-15}}$ (67.9%), followed by the often co-detected $bla_{\text{TEM-1B}}$ (39.3%). No *mcr* or carbapenemase genes were detected. The majority of the strains belonged to phylogroups B2 (38.4%) and A (32.1%), carrying *fimH27* (25%) and *fimH30* (19.6%). A core-genome MLST minimum spanning tree did not reveal clusters containing strains from both the asylum seekers and the control group. Five clusters were formed within the asylum seeker group, by strains isolated from people originating from different countries.

Conclusion

The most frequently isolated clones in this study were isolated on a regular basis within the Dutch population before the increase in the asylum seeker population. No *mcr*- or carbapenemase-producing clones were detected among the asylum seeker population. Minor clustering was observed amongst the asylum seeker strains.

INTRODUCTION

Increased numbers of refugees and asylum seekers have entered Europe during the last decade. At the end of 2018, the United Nations High Commissioner for Refugees reported nearly 6.5 million refugees and migrants residing in Europe[1]. According to the Immigration and Naturalization Service of the Ministry of Justice and Security, 196519 asylum seekers entered the Netherlands from January 2013 to December 2018. Main countries of origin include the Syrian Arab Republic, Afghanistan, Iraq, Iran and Eritrea[2].

This increase in displaced populations has public health implications. The health needs of refugees and asylum seekers require coordinated efforts from public health institutions. Medical care of refugees and asylum seekers can be challenging for public health systems and hospitals[3]. Although data on the epidemiology of multi-drug resistant organisms (MDRO) in most of the countries of origin are limited, studies have showed an increased MDRO prevalence amongst refugees and asylum seekers. A recently published systematic review and meta-analysis on antimicrobial resistance among migrants in Europe, showed a pooled prevalence of any detected antimicrobial resistance carriage or infection of 25.4% (95% CI 19.1–31.8). The pooled prevalence of MDR Gram-negative bacteria was 27.2% (95% CI 17.6–36.8)[4].

The need for adequate and timely MDRO detection and, subsequently, the implementation of infection prevention measures regarding refugee inpatients is imperative. WGS has proved to be a valuable tool for microbial analysis on a molecular level and for MDRO outbreak investigation. During the last decade, WGS has been increasingly integrated in microbiology laboratories as part of the daily routine diagnostics, as it became easier, faster and cheaper to use[5]. This technique combined with bioinformatics tools can provide, in less than 48 h, an abundance of valuable information regarding MDRO, including detection, identification, genetic resistance profile, genotype and epidemiological typing. Further analysis of the data can also determine genetic and phylogenetic relatedness amongst strains, revealing clustering and aiding outbreak investigation[6,7].

The main mechanism of resistance to β-lactams in *Escherichia coli* strains is production of ESBLs, a group of enzymes mainly encoded by CTX-M, TEM and SHV variants[8]. During the past decade, $bla_{\text{CTX-M}}$ genes have been increasingly detected in Gram-negative bacteria, including *E. coli* worldwide, leading to a 'CTX-M pandemic' situation[9]. This rapid spread of certain CTX-M-producing *E. coli* lineages brings

along difficulties in typing. Conventional typing methods, such as PFGE and MLST, do not have the discriminatory power to identify clusters of dissemination. Even next-generation sequencing ('NGS')-based typing, which has higher discriminatory power, does not always provide conclusive proof of dissemination and should always be interpreted in combination with epidemiological data. Additional methods, such as typing of *fimH* genes, are useful to subtype certain lineages[10]. In addition, sequences of epidemiologically unrelated isolates, so-called context isolates, should be added to the analysis to provide insight into the genetic background of the bacterial population[11].

In this study, we evaluated the molecular profiles, including STs, *fim* types, phylogroups and resistomes, of ESBL-producing *E. coli* (ESBL-*E. coli*) strains isolated from hospitalized asylum seekers in 2016. We compared the molecular epidemiology of the isolates from the refugees with a collection of ESBL-*E. coli* strains from the Dutch–German border region, from hospitalized patients and a community population in 2012, before the number of refugees started to increase.

MATERIALS AND METHODS

Study design

When entering the Netherlands, all asylum seekers are appointed to an asylum seeker centre (ASC) and are registered under the ASC's address. Asylum seekers, included in the study, were identified by the ASC address they resided at. Data on patient characteristics were retrospectively collected from the Certe laboratory system. Study material included screening samples for MDRO carriage before admission (throat, rectum and nose) and clinical samples (e.g. blood, wounds and urogenital) from asylum seekers. All of these samples were obtained as part of the standard care.

Study population

We included asylum seekers, hospitalized in the northern part of the Netherlands from 1 January to 31 December 2016, who tested positive for ESBL-*E. coli* strains. Demographic data, such as age, sex and country of origin, were collected from the laboratory system and the healthcare system for asylum seekers. All ESBL-*E. coli* strains isolated from the study population were included in the group of asylum seeker strains. Duplicate strains with the same molecular, phenotypic and genotypic profile that were from the same asylum seeker were excluded.

Bacterial identification and antimicrobial resistance mechanism detection

ESBL-*E. coli* strains from asylum seekers were obtained in the Certe laboratory. This laboratory performs routine microbiological analyses for primary and secondary medical care in the north-east of the Netherlands, including the ASC population in this part of the country. Screening and clinical samples were cultured in a variety of selective (solid) media used for MDRO detection, including MacConkey agar with 0.5 mg/L ciprofloxacin and 2 mg/L gentamicin (Mediaproducts BV, Groningen, The Netherlands), ChromID ESBL agar and ChromID Carbapenemase agar (both from bioMérieux, Marcy-l'Étoile, France). The presence of ESBL was confirmed with cefotaxime/clavulanate, ceftazidime/clavulanate and cefepime/clavulanate Etests (bioMérieux). Possible carbapenemase-producing Enterobacterales (CPE) were confirmed by CIM test and PCR (Check-Direct CPE assay, Check-Points, Wageningen, The Netherlands) and typed by the national reference network for CPE at the RIVM (National Institute for Public Health), as part of standard care.

Antimicrobial phenotype detection

Susceptibility to amikacin, amoxicillin/clavulanic acid, ampicillin/sulbactam, cefepime, cefotaxime, ceftazidime, ciprofloxacin, colistin, ertapenem, fosfomycin, gentamicin, imipenem, levofloxacin, meropenem, nitrofurantoin, piperacillin/tazobactam, tigecycline and trimethoprim/sulfamethoxazole was determined using Vitek 2 (bioMérieux). EUCAST guidelines were used for interpretation of MICs.

Control group isolates

The control isolate collection consisted of 41 ESBL-*E. coli* from hospitalized patients and people in the community in the Netherlands and 11 ESBL-*E. coli* strains from hospitalized patients in Germany[12] The isolates were collected in 2012 and were used as context isolates in the genomic comparisons. All strains included in the control group were analysed using the same workflow as the asylum seeker group strains.

DNA isolation

A total of 112 frozen ESBL-*E. coli* strains isolated from unique asylum seekers were recultured and incubated for 24 h at 37°C. DNA was extracted using the DNeasy UltraClean Microbial Kit (MoBio Laboratories, Carlsbad, CA, USA), according to the manufacturer's instructions. A 5µL aliquot of each isolate was suspended with 300 µL of PowerBead solution. DNA purity was measured using a NanoDrop 2000C

spectrophotometer (Thermo Fisher, Waltham, MA, USA). DNA concentration was measured using a Qubit 2.0 fluorometer, using the double-stranded DNA BR Assay Kit (Life Technologies, Carlsbad, CA, USA).

Whole Genome Sequencing

Prior to library preparation, isolated DNA was diluted to a concentration of 0.2 ng/µL. DNA library preparation was performed with the Nextera XT v.01 (Illumina Inc., San Diego, CA) kit using 5 µL of diluted DNA according to the manufacturer's instructions. Libraries were sequenced on an MiSeq sequencer (Illumina Inc.) aiming to generate 250 bp paired-end reads.

Quality check and WGS data analysis

Trimming and *de novo* assembly was performed using CLC Genomics Workbench v.10.1.2 (QIAGEN, Hilden, Germany). A minimum Phred score (Qscore) of 30 was used. Six parameters were checked for assembly quality: number of contigs <1000, N50 >15000, maximum contig length >50000, percentage of reads used for the assembly >90%, coverage >30× and percentage of the expected genome size >90% to <115%.

The assembled genomes were uploaded to SeqSphere v.5.5.1 (Ridom GmbH, Münster, Germany) for phylogenetic relatedness investigation. A minimum spanning tree based on allelic mismatch between the isolates was designed. A maximum of 10 allelic differences was considered as clonal clustering.

SNP-based neighbour joining trees were constructed based on the genome sequences using Ridom SeqSphere+ version 5.1.0 (Münster, Germany) with default settings. The genomes were analysed using an *ad hoc E. coli* scheme based on 2764 targets, including 242851 bp.

Assembled genomes were uploaded to the web tools ResFinder 3.1 to identify acquired resistance genes[13] and FimTyper 1.0 to determine *fim* type[10]. Phylogroups were determined via the EzClermont web app and command-line tool[14,15].

Sequences are publicly available at the ENA database (study accession number PRJEB36686).

Statistical analysis

Data were collected in and analysed with SPSS (version 2.23). Descriptive statistics were used for the general characteristics of the study population.

Ethics

This study was evaluated by the Ethics Committee and approval was waived in accordance with Dutch legislation owing to its retrospective nature (University Medical Centre Groningen, METc number 2016/516). No written informed consent was obtained from patients for the use of retrospective data. Patient information was anonymized and de-identified prior to analysis.

RESULTS

General characteristics of the study population

We evaluated single ESBL-*E. coli* isolates from 112 asylum seekers. General characteristics of the study population and the included samples are described in Table 1.

TABLE 1. General characteristics of the study population and the included samples; *N*=112

Female, *n* (%)	75 (67)
Age (years), median (IQR)	28.0 (20.4–36.1)
Number of days in the Netherlands, median (IQR)	192 (77–347)
Country of origin, *n* (%)	
Syria	40 (35.7)
Iraq	15 (13.4)
Iran	12 (10.7)
Afghanistan	9 (8.0)
Eritrea	6 (5.4)
other from Europe	6 (5.4)
other from Eastern Europe/Russia	4 (3.6)
other from Asia	8 (7.1)
other from Africa	9 (8.0)
Samples, *n* (%)	
rectal	101 (90.2)
urine	6 (5.4)
skin	2 (1.8)
sputum	1 (0.9)
nasal	1 (0.9)
stool	1 (0.9)

Routinely measured resistance

Antimicrobial susceptibility of the strains to different antibiotic agents, routinely tested in the Certe laboratory, is described in Table S1 (available as Supplementary data at *JAC* Online).

All of the isolates were resistant to penicillins, cephalosporins and combinations of penicillins and β-lactamase inhibitors. Also, 56.3% of the isolates were resistant to trimethoprim/sulfamethoxazole. Resistance to ciprofloxacin was observed in 31.3% of the isolates. Regarding aminoglycosides, 27.7% and 33.0% of the isolates were resistant to gentamicin and tobramycin, respectively. No isolate was resistant to meropenem or imipenem. All isolates were susceptible to fosfomycin and colistin.

ST and genotypic profile

The most frequent ST of the asylum seeker isolates was ST131 (21.4%), followed by ST10 (17.0%), ST38 (8.0%) and ST69 (8.9%). Among the control group isolates, the most frequent ST was ST38 (15.4%), followed by ST10 and ST131 (both 11.5%) and ST58 (7.7%). Table 2 shows the STs of the asylum seeker isolates and the $bla_{\text{CTX-M}}$ resistance genes carried by the isolates for each ST.

TABLE 2. STs of the asylum seeker isolates and the $bla_{\text{CTX-M}}$ resistance genes carried by the isolates for each ST

		$bla_{\text{CTX-M}}$ resistance gene, *n* (%)				
ST	**Total, *N* (%)**	$bla_{\text{CTX-M-15}}$	$bla_{\text{CTX-M-27}}$	$bla_{\text{CTX-M-3}}$	$bla_{\text{CTX-M-14}}$	$bla_{\text{CTX-M-14b}}$
ST131	24 (21.4)	12 (50.0)	7 (29.2)	1 (4.2)	0 (0)	0 (0)
ST10	19 (17.0)	16 (84.2)	0 (0)	2 (10.5)	1 (5.3)	0 (0)
ST69	10 (8.9)	8 (80)	0 (0)	1 (10)	0 (0)	0 (0)
ST38	9 (8.0)	1 (11.1)	1 (11.1)	0 (0)	1 (11.1)	3 (33.3)
ST12	7 (6.3)	7 (100.0)	0 (0)	0 (0)	0 (0)	0 (0)
ST120	4 (3.6)	3 (75.0)	0 (0)	0 (0)	0 (0)	0 (0)
ST93	4 (3.6)	4 (100.0)	0 (0)	0 (0)	0 (0)	0 (0)
ST1193	3 (2.7)	2 (66.7)	0 (0)	0 (0)	0 (0)	0 (0)
ST73	3 (2.7)	2 (66.7)	0 (0)	0 (0)	0 (0)	0 (0)
ST648	2 (1.8)	2 (100.0)	0 (0)	0 (0)	0 (0)	0 (0)
ST3877	2 (1.8)	2 (100.0)	0 (0)	0 (0)	0 (0)	0 (0)
ST58	2 (1.8)	2 (100.0)	0 (0)	0 (0)	0 (0)	0 (0)
Other	23 (20.5)	14 (60.9)	1 (4.3)	1 (4.3)	2 (8.7)	0 (0)

Distribution of *bla*$_{CTX-M}$ resistance genes harboured by the isolates from asylum seekers and the control group can be seen in Figure 1.

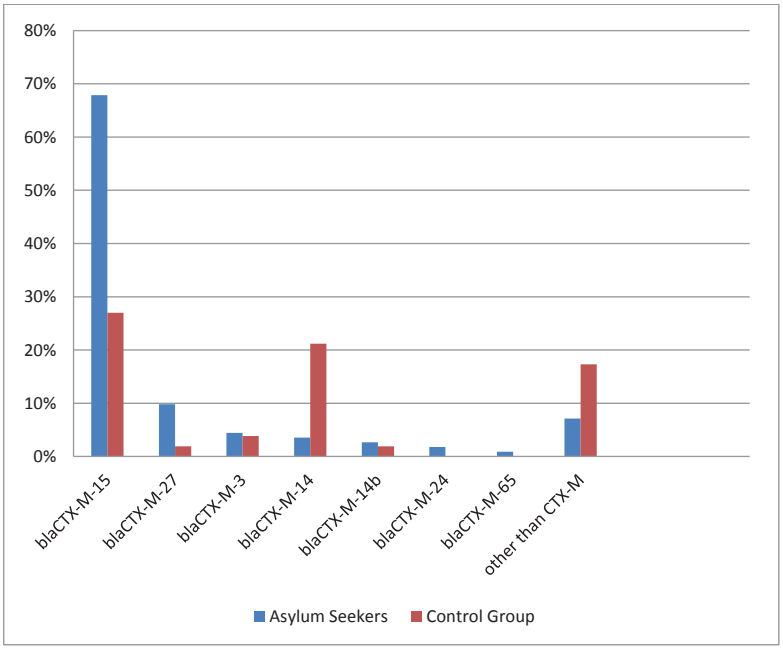

FIGURE 1. Distribution of the most frequently detected *bla*$_{CTX-M}$ genes among the asylum seeker and control group isolates.

The most frequently observed CTX-M gene for β-lactam resistance was *bla*$_{CTX-M-15}$ for both groups, followed by *bla*$_{CTX-M-27}$ for the asylum seekers and *bla*$_{CTX-M-1}$ for the control group. Other, non-CTX-M β-lactam resistance genes detected in the asylum seeker isolates were *bla*$_{TEM-1B}$ (*n*=44, 39.3%), *bla*$_{OXA-1}$ (*n*=11, 9.8%), *bla*$_{SHV-12}$ (*n*=2), *bla*$_{TEM-33}$ (*n*=2), *bla*$_{DHA-1}$ (*n*=2), *bla*$_{TEM-1C}$ (*n*=1) and *bla*$_{CMY-60}$ (*n*=1).

All of the asylum seeker isolates carried resistance genes related to more than one antibiotic group, including aminoglycosides, fluoroquinolones, sulphonamides and trimethoprim. Regarding aminoglycoside resistance, 44 isolates harboured *strA*, 43 harboured *strB*, 42 harboured *addA5* and 21 harboured *acc(3)-IId*. Main genes carried by the isolates that encoded quinolone resistance were *qnrS1* (*n*=26) and *aac(6')Ib-cr* (*n*=10). For sulphonamide resistance, 48 isolates carried *sul1* and 40

isolates carried *sul2*. Lastly, the main trimethoprim resistance genes detected were *dfrA17* (*n*=44) and *dfrA14* (*n*=14). Of note, no *mcr* and carbapenemase genes were detected.

Phylogroup and fim type

Asylum seeker isolates belonged primarily to phylogroups B2 (*n*=43, 38.4%) and A (*n*=36, 32.1%). The remaining isolates belonged to phylogroups D (*n*=24, 21.4%), B1 (*n*=6, 5.4%) and F (*n*=3, 2.7%).

Subtyping of *fimH* alleles of isolates from asylum seekers showed that *fimH27* was the most frequent type (*n*=28, 25%), followed by *fimH30* (*n*=22, 19.6%) and *fimH5* (*n*=6, 5.4%). Thirteen isolates (11.6%) did not carry any *fim* gene. The remaining isolates carried a wide variety of different *fim* genes. Of note, 19 out of the 24 isolates that belonged to ST131 carried *fimH30* and 8 out of the 19 isolates that belonged to ST10 carried *fimH27*.

Analysis of the core-genome MLST (cgMLST) neighbour joining tree, including asylum seeker and control group isolates, is shown in Figure 2. Furthermore, the cgMLST neighbour joining tree is shown in Figure S1 in rectangular form, including metadata, such as country of origin of the asylum seekers, isolate ST and isolate phylogroup (given in the columns next to the tree).

Phylogenetic relatedness and cluster analysis

A minimum spanning tree of the asylum seeker and control group isolates can be seen in Figure S2. The observed allelic distance ranged from 0 to 2371 alleles.

Cluster analysis revealed five clusters within the asylum seeker group isolates (Figure S2). Cluster 1 consisted of six isolates belonging to ST69, phylogroup D, subtype *fimH27* and carrying $bla_{\text{CTX-M-15}}$ (Figure 2). Two of the isolates were from asylum seekers originating from Syria and the remaining four were from asylum seekers originating from Palestine, Afghanistan, Iraq and Yugoslavia. The isolates from the Syrian and Iraqi asylum seekers were isolated from rectal and skin samples, cultured a day apart, respectively, and the isolates from the Palestinian and Afghan asylum seekers came from sputum and urine samples, respectively, cultured 17 days apart. Cluster 2 was formed by five isolates belonging to ST10, phylogroup A, subtype *fimH27* and carrying $bla_{\text{CTX-M-15}}$ (Figure 2). All isolates were obtained from asylum seekers originating from different countries, namely Syria, Iraq, Eritrea, Turkey and Benin. The isolates from the Syrian and Iraqi asylum seekers were isolated from rectal samples, cultured 4 days apart. Cluster 3 consisted of four isolates belonging

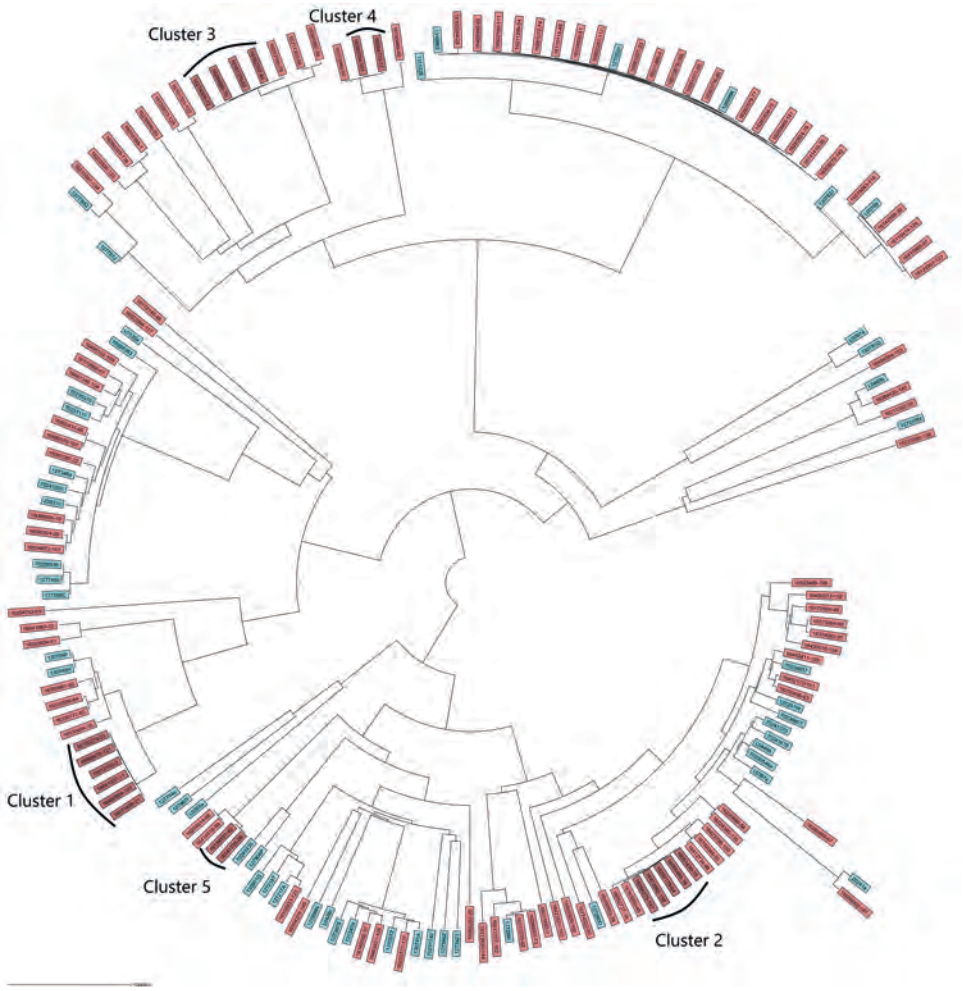

FIGURE 2. cgMLST neighbor joining tree, including asylum seeker and control group isolates. Genomes were analysed using an *ad hoc E. coli* scheme based on 2764 targets, including 242851 bp. Control group isolates were from health institutions near the Dutch–German border region. Isolates that formed clusters in further phylogenetic analysis are indicated in dark pink.

to ST12, phylogroup B2, no *fim* subtype and carrying $bla_{\text{CTX-M-15}}$ (Figure 2). Two of the strains were isolated from Syrian asylum seekers, one from a Mongolian asylum seeker and one from an Afghan asylum seeker. One of the isolates that was from a Syrian asylum seeker and the isolate that was from an Afghan asylum seeker were isolated from rectal samples, cultured a week apart. Cluster 4 included two isolates belonging to ST1193, phylogroup B2, subtype *fimH64* and carrying $bla_{\text{CTX-M-15}}$

(Figure 2). One was isolated from a Syrian asylum seeker and the other from an Iranian; they were isolated from urine and rectal samples, respectively, cultured 7 months apart. Cluster 5 consisted of two isolates belonging to ST120, phylogroup A, subtype *fimH237* and carrying $bla_{CTX\text{-}M\text{-}15}$ (Figure 2). The two isolates were from a Syrian asylum seeker and an Eritrean asylum seeker; they were isolated from rectal samples, cultured 10 days apart. No clusters contained isolates belonging to both asylum seekers and control group isolates.

DISCUSSION

A total of 112 ESBL-*E. coli* strains isolated from asylum seekers were analysed using WGS in order to investigate their phylogenetic relatedness and possible transmission within the asylum seeker population in the northern part of the Netherlands. The asylum seeker study population originated mainly from Syria and had been residing in the Netherlands for a median of 192 days.

All isolates were phenotypically resistant to β-lactams and exhibited various resistance profiles, with all of them being resistant to at least one more antibiotic group, such as aminoglycosides, quinolones and sulphonamides. The genes that encode resistance to these antibiotic agents are often located on plasmids that can co-harbour different resistance genes and can be horizontally transferred amongst Enterobacterales, like *E. coli*, rendering the strains MDR[16].

The majority of the isolates belonged to ST131 and ST10, and harboured a $bla_{CTX\text{-}M\text{-}15}$ gene. This is in accordance with the epidemiological profile of the high-risk ST131 $bla_{CTX\text{-}M\text{-}15}$ clone. ST131 $bla_{CTX\text{-}M\text{-}15}$ is currently globally disseminated and is identified as the most widespread CTX-M ESBL enzyme worldwide[17,18]. The Netherlands has also been affected by the ST131 $bla_{CTX\text{-}M\text{-}15}$ clone. In a recently published study conducted in Dutch hospitals, between 2014 and 2016, the dominant clone found among ESBL-*E. coli* blood isolates was ST131 carrying $bla_{CTX\text{-}M\text{-}15}$[19]. Furthermore, in a study conducted in the Netherlands in 2016, the clone was isolated among community-associated and hospitalized patients,[20] indicating that the clone existed in both the community and hospitals in the Netherlands before the number of refugees started to increase in 2015 and 2016.

The majority of the study isolates harboured $bla_{CTX\text{-}M\text{-}15}$, regardless of the ST they belonged to. Even though strains carrying $bla_{CTX\text{-}M\text{-}15}$ have been reported all over Europe, strains carrying this gene are isolated at a higher rate in Middle Eastern, Asian and African regions[21]. Furthermore, epidemiological data on the distribution

of such strains indicate that African and Asian regions could serve as a reservoir and facilitate global dissemination[22]. A German study that investigated the antibiotic resistomes of refugees reported high prevalence rates for β-lactamase genes; mainly bla_{TEM}, bla_{CTX-M} group 1 and bla_{SHV}[23]. Another German study reported high detection of bla_{CTX-M} group 1 genes, followed by bla_{TEM} and bla_{SHV} among ESBL-producing Enterobacteriaceae isolates from Libyan and Syrian patients[24]. Furthermore, a study performed in Saudi Arabia showed a prevalence of $bla_{CTX-M-15}$ or $bla_{CTX-M-14}$ of 60% among ST131 uropathogenic *E. coli* strains[25]. In addition, an Iranian study, published in 2017, demonstrated a high prevalence of ST131 $bla_{CTX-M-15}$ amongst clinical *E. coli* strains[26]. High prevalence of strains carrying these genes, amongst asylum seekers from Iran, Syria and Afghanistan, was also documented in our study.

Despite the fact that some clustering among the asylum seekers isolates was observed, no clear pattern of transmission was documented. Isolates that exhibited close phylogenetic relatedness formed five clusters. As expected, isolates within each cluster exhibited identical genetic characteristics, such as ST, phylogroup and *fim* type. However, isolates included within each cluster did not show a clear epidemiological link, since they were isolated from asylum seekers mostly originating from different countries. Furthermore, even though certain isolates in clusters 1, 2, 3 and 5 were isolated within 10 days or less, clear epidemiological links cannot be hypothesized without additional information, such as department and institution of hospitalization, ASC of residence and countries they have travelled through before entering the Netherlands. Due to limited clustering and wide dispersion of the origin of the asylum seekers carrying the isolates within each cluster, no conclusion can be drawn regarding the geographical epidemiology and origin of the isolates.

A limited number of studies have previously sequenced MDROs in a refugee/asylum seeker patient population[27,28]. To our knowledge, this is the first study to investigate ESBL-*E. coli* strains isolated from asylum seekers using WGS on a large scale documenting various genetic characteristics, such as STs, genotypic resistance profiles and phylogenetic relatedness. This information is still scarce in related literature and can help to optimize treatment, hospital hygiene strategies and infection control measures. Furthermore, our study population exhibited a large variation in age, number of days in the Netherlands and country of origin, reflecting the main countries from which migrants originate, namely Syria, Afghanistan and Iraq[1].

Due to the retrospective aspect of this study, we did not have access to important information, such as travelling and antibiotic consumption history. In addition,

information regarding asylum seeker hospitalization, such as reason of admission, department of admission, duration of hospitalization and treatment given, was not available. Furthermore, we had no access to data regarding the specific ASCs where our study population resided, after their arrival in the Netherlands. Close contact within a facility can lead to transmission of MDRO. In our study, no clear pattern of transmission was observed.

Conclusions

The most frequently isolated clones in the study are already detected on a regular basis within the Dutch population. No *mcr*- or carbapenemase-producing clones were detected among the asylum seeker population. No clustering between asylum seekers and control group strains was observed.

Even though no assumptions can be made on whether transmission within the asylum seeker population occurs or not, small clustering within the asylum seeker strains could be an indication. Based on the results of this study, there is no clear evidence whether asylum seekers obtained their MDRO in their country of origin, during their journey to the Netherlands or after their arrival in the Netherlands. Asylum seekers originating from the same country showed a large variability in resistance and phylogenetic relatedness. Further research on the genetic characteristics of MDRO isolates carried by asylum seekers could reveal important information on transmission and cluster formation.

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Transparency declarations

J.W.R. is currently an employee of IDbyDNA. IDbyDNA did not have any influence on the interpretation of reviewed data and conclusions drawn, or on the drafting of the manuscript, and did not (financially) support the study. All other authors: none to declare.

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SUPPLEMENTARY DATA

SUPPLEMENTARY TABLE S1

	MIC (mg/L)									
Isolate	**AMOX**	**AMC**	**AMP**	**PITA**	**CZOL**	**CFEP**	**CFUR**	**CFOX**	**CFOT**	**CFTA**
16010398-1	R	4 [R]	≥32 [R]	≤4 [R]	≥64 [R]	2 [I]	≥64 [R]	≤4 [S]	≥64 [R]	4 [R]
16011687-2	R	16 [R]	≥32 [R]	≤4 [R]		2 [R]	≥64 [R]	≤4 [R]	32 [R]	16 [R]
16012103-3	R	8 [R]	≥32 [R]	≤4 [R]		≥64 [R]	≥64 [R]	≤4 [R]	≥64 [R]	16 [R]
16011860-4	R	4 [R]	≥32 [R]	≤4 [R]		2 [R]	≥64 [R]	16 [R]	32 [R]	4 [R]
16041337-11	R	8 [R]	≥32 [R]	≤4 [R]	≥64 [R]	8 [R]	≥64 [R]	≤4 [R]	≥64 [R]	16 [R]
16041689-12	R	8 [R]	≥32 [R]	≤4 [R]		4 [R]	≥64 [R]	≤4 [R]	≥64 [R]	8 [R]
16051430-15	R	4 [R]	≥32 [R]	≤4 [R]		≤1 [R]	≥64 [R]	≤4 [R]	16 [R]	≤1 [R]
16052737-16	R	8 [R]	≥32 [R]	≤4 [R]		≤1 [R]	≥64 [R]	≤4 [R]	≥64 [R]	≤1 [R]
16054770-17	R	8 [R]	≥32 [R]	≤4 [R]		4 [R]	≥64 [R]	≤4 [R]	≥64 [R]	4 [R]
16055468-18	R	4 [R]	≥32 [R]	≤4 [R]		≤1 [R]	≥64 [R]	≤4 [R]	8 [R]	≤1 [R]
16060606-19	R	≥32 [R]	≥32 [R]	64 [R]		2 [R]	≥64 [R]	8 [R]	16 [R]	≤1 [R]
16065222-20	R	≥32 [R]	≥32 [R]	≥128 [R]		≤1 [R]	32 [R]	≤4 [R]	8 [R]	16 [R]
16071499-21	R	4 [R]	≥32 [R]	≤4 [R]		8 [R]	≥64 [R]	≤4 [R]	≥64 [R]	4 [R]
16081587-22	R	≥32 [R]	≥32 [R]	≥128 [R]		≤1 [R]	≥64 [R]	8 [R]	8 [R]	≤1 [R]
16081927-23	R	≥32 [R]	≥32 [R]	≥128 [R]		≤1 [R]	≥64 [R]	8 [R]	8 [R]	≤1 [R]
16090304-26	R	16 [R]	≥32 [R]	≤4 [R]		16 [R]	≥64 [R]	32 [R]	≥64 [R]	4 [R]
16100264-28	R	≥32 [R]	≥32 [R]	8 [R]		≥64 [R]	≥64 [R]	≤4 [R]	≥64 [R]	4 [R]
16100503-29	R	≥32 [R]	≥32 [R]	≤4 [R]		2 [R]	≥64 [R]	≥64 [R]	≥64 [R]	4 [R]
16100279-31	R	4 [R]	≥32 [R]	≤4 [R]		8 [R]	≥64 [R]	≤4 [R]	≥64 [R]	16 [R]
16130454-35	R	4 [R]	≥32 [R]	≤4 [R]		2 [R]	≥64 [R]	≤4 [R]	≥64 [R]	4 [R]
16141410-36	R	4 [R]	≥32 [R]	≤4 [R]		32 [R]	≥64 [R]	8 [R]	≥64 [R]	16 [R]
16140692-37	R	8 [R]	≥32 [R]	≤4 [R]		2 [R]	≥64 [R]	≤4 [R]	≥64 [R]	16 [R]
16141735-38	R	≥32 [R]	≥32 [R]	64 [R]		2 [R]	≥64 [R]	≤4 [R]	≥64 [R]	16 [R]
16142558-39	R	8 [R]	≥32 [R]	≤4 [R]		8 [R]	≥64 [R]	≤4 [R]	≥64 [R]	16 [R]
16150469-40	R	16 [R]	≥32 [R]	≤4 [R]		≤1 [R]	16 [R]	≤4 [R]	4 [R]	16 [R]
16154590-41	R	4 [R]	≥32 [R]	≤4 [R]		≤1 [R]	≥64 [R]	≤4 [R]	16 [R]	4 [R]
16154551-42	R	≥32 [R]	≥32 [R]	≥128 [R]		8 [R]	≥64 [R]	16 [R]	≥64 [R]	16 [R]
16162107-44	R	4 [R]	≥32 [R]	≤4 [R]		2 [R]	≥64 [R]	≤4 [R]	32 [R]	4 [R]
16163200-45	R	8 [R]	≥32 [R]	≤4 [R]		4 [R]	≥64 [R]	≤4 [R]	≥64 [R]	8 [R]
16170114-46	R	4 [R]	≥32 [R]	≤4 [R]		2 [R]	≥64 [R]	≤4 [R]	≥64 [R]	4 [R]
16170588-47	R	4 [R]	≥32 [R]	≤4 [R]		2 [R]	≥64 [R]	≤4 [R]	≥64 [R]	4 [R]
16172140-48	R	4 [R]	≥32 [R]	≤4 [R]		≤1 [R]	≥64 [R]	≤4 [R]	8 [R]	4 [R]
16172604-49	R	4 [R]	≥32 [R]	≤4 [R]		2 [R]	≥64 [R]	≤4 [R]	32 [R]	4 [R]
16174022-50	R	16 [R]	≥32 [R]	≤4 [R]		2 [R]	≥64 [R]	≤4 [R]	32 [R]	16 [R]
16181376-52	R	4 [R]	≥32 [R]	≤4 [R]		2 [R]	≥64 [R]	≤4 [R]	≥64 [R]	4 [R]
16192048-53	R	4 [R]	≥32 [R]	≤4 [R]		≤1 [R]	≥64 [R]	≤4 [R]	8 [R]	≤1 [R]
16211299-54	R	4 [R]	≥32 [R]	≤4 [R]		≥64 [R]	≥64 [R]	8 [R]	≥64 [R]	16 [R]
16211267-55	R	8 [R]	≥32 [R]	≤4[R]		2 [R]	≥64 [R]	16 [R]	≥64 [R]	16 [R]
16211303-56	R	4 [R]	≥32 [R]	≤4[R]		≥64 [R]	≥64 [R]	≤4 [R]	≥64 [R]	16 [R]
16230686-58	R	4[R]	≥32 [R]	≤4[R]		≤1 [R]	≥64 [R]	≤4 [R]	≥64 [R]	2 [R]
16230696-59	R	8 [R]	≥32 [R]	≤4[R]		2 [R]	≥64 [R]	8 [R]	≥64 [R]	4 [R]
16250495-63	R	16 [R]	≥32 [R]	≤4[R]		≤1 [R]	≥64 [R]	≤4 [R]	8 [R]	4 [R]
16250179-64	R	4 [R]	≥32 [R]	≤4[R]		≤1 [R]	≥64 [R]	≤4 [R]	8 [R]	2 [R]
16251571-65	R	≥32 [R]	≥32 [R]	8 [R]		≥64 [R]	≥64 [R]	8 [R]	≥64 [R]	16 [R]

CFTR	GENT	TOBR	TRIM	SXT	NITR	FOSF	CIPR	IMIP	MERO	COL
R	≤1 [S]	≤1 [S]	≤0.5 [S]	≤20 [S]	≤16 [S]	≤16 [S]	≤0.25 [S]		≤0.25 [S]	
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320	≤16 [S]		≥4 [R]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≤20 [S]	≤16 [S]		≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320	≤16 [S]		≥4 [R]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	8 [R]	≥320 [R]	64 [S]	≤16 [S]	≥4 [R]		≤0.25 [S]	
R	≥16 [R]	8 [R]	≥16 [R]	≥320 [R]	≤16 [S]		≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320 [R]	≤16 [S]		0.5 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≤0.5 [S]	≤20 [S]	≤16 [S]		≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≥16 [R]	8 [R]	≥16 [R]	≥320 [R]	≤16 [S]		≥4 [R]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≤20 [S]	≤16 [S]		0.5 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≥16 [R]	8 [R]	≥16 [R]	≥320 [R]	≤16 [S]		0.5 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≤20 [S]	≤16 [S]		1 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≤20 [S]	≤16 [S]		≥4 [I]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≥16 [R]	8 [R]	≥16 [R]	≥320 [R]	≤16 [S]		≤0.25	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≥16 [R]	8 [R]	≥16 [R]	≥320 [R]	≤16 [S]		≤0.25	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320 [R]	64 [S]		≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≥16 [R]	≥16 [R]	≥320 [R]	≤16 [S]		≥4 [R]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≤20 [S]	≤16 [S]		≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≥16 [R]	4 [R]	≥16 [R]	≤20 [S]	≤16 [S]		≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≤20 [S]	≤16 [S]		≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≤0.5 [S]	≤20 [S]	≤16 [S]		≥4 [R]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320 [R]	≤16 [S]		0.5 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≥16 [R]	8 [R]	≤0.5 [S]	≤20 [S]	≤16 [S]		0.5 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320 [R]	≤16 [S]		0.5 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320 [R]	≤16 [S]		≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320 [R]	≤16 [S]		≥4 [R]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≤0.5 [S]	≤20 [S]	≤16 [S]		0.5 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≥16 [R]	4 [R]	≤0.5 [S]	≤20 [S]	≤16 [S]		≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320 [R]	≤16 [S]		≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≤0.5 [S]	≤20 [S]	≤16 [S]		≥4 [R]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≥16 [R]	8 [R]	≥16 [R]	≥320 [R]	32 [S]		≥4 [R]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320 [R]	≤16 [S]		≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≤0.5 [S]	≤20 [S]	≤16 [S]		≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320 [R]	≤16 [S]		≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≥16 [R]	8 [R]	≤0.5 [S]	≤20 [S]	≤16 [S]		≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≤0.5 [S]	≤20 [S]	≤16 [S]		≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≤0.5 [S]	≤20 [S]	≤16 [S]		≥4 [R]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320 [R]	≤16 [S]		≥4 [R]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≥16 [R]	8 [R]	≤0.5 [S]	≤20 [S]	≤16 [S]		≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≤0.5 [S]	≤20 [S]	≤16 [S]		≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≥16 [R]	8 [R]	≤0.5 [S]	≤20 [S]	≤16 [S]		≥4 [R]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320 [R]	≤16 [S]		≥4 [R]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≥16 [R]	8 [R]	≥16 [R]	≥320 [R]	≤16 [S]		≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≥16 [R]	≥16 [R]	≥320 [R]	≤16 [S]		≥4 [R]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]

SUPPLEMENTARY TABLE S1. Continued

	MIC (mg/L)									
Isolate	**AMOX**	**AMC**	**AMP**	**PITA**	**CZOL**	**CFEP**	**CFUR**	**CFOX**	**CFOT**	**CFTA**
16254014-66	R	4 [R]	≥32 [R]	≤4 [R]		≤1 [R]	≥64 [R]	≤4 [R]	8 [R]	4 [R]
16260469-67	R	8 [R]	≥32 [R]	≤4 [R]		2 [R]	≥64 [R]	≤4 [R]	≥64 [R]	4 [R]
16254762-69	R	8 [R]	≥32 [R]	≤4 [R]		≥64 [R]	≥64 [R]	≤4 [R]	≥64 [R]	16 [R]
16274308-72	R	4 [R]	≥32 [R]	≤4 [R]		2 [R]	≥64 [R]	≤4 [R]	≥64 [R]	4 [R]
16280603-73	R	4 [R]	≥32 [R]	≤4 [R]		2 [R]	≥64 [R]	≤4 [R]	≥64 [R]	4 [R]
16281072-74	R	4 [R]	≥32 [R]	≤4 [R]		2 [R]	≥64 [R]	8 [R]	≥64 [R]	4 [R]
16281834-75	R	≥32 [R]	≥32 [R]	64 [R]		≥64 [R]	≥64 [R]	8 [R]	≥64 [R]	≥64 [R]
16284688-76	R	4 [R]	≥32 [R]	≤4 [R]		2 [R]	≥64 [R]	≤4 [R]	≥64 [R]	4 [R]
16292579-77	R	8 [R]	≥32 [R]	≤4 [R]		2 [R]	≥64 [R]	≤4 [R]	32 [R]	4 [R]
16293199-78	R	8 [R]	≥32 [R]	≤4 [R]		2 [R]	≥64 [R]	≤4 [R]	32 [R]	4 [R]
16293824-79	R	16 [R]	≥32 [R]	8 [R]		≥64 [R]	≥64 [R]	≤4 [R]	≥64 [R]	16 [R]
16303776-80	R	16 [R]	≥32 [R]	≤4 [R]		4 [R]	≥64 [R]	8 [R]	≥64 [R]	16 [R]
16303834-81	R	8 [R]	≥32 [R]	≤4 [R]		2 [R]	≥64 [R]	≤4 [R]	≥64 [R]	16 [R]
16311239-82	R	4 [R]	≥32 [R]	≤4 [R]		2 [R]	≥64 [R]	≤4 [R]	≥64 [R]	4 [R]
16330172-83	R	4 [R]	≥32 [R]	≤4 [R]		≤1 [R]	≥64 [R]	≤4 [R]	8 [R]	2 [R]
16333596-84	R	4 [R]	≥32 [R]	≤4 [R]		≤1 [R]	≥64 [R]	≤4 [R]	8 [R]	≤1 [R]
16350431-86	R	4 [R]	≥32 [R]	≤4 [R]		2 [R]	≥64 [R]	16 [R]	≥64 [R]	4 [R]
16373084-90	R	≥32 [R]	≥32 [R]	≤4 [R]			≥64 [R]	≤4 [R]	≥64 [R]	4 [R]
16374082-91	R	16 [R]	≥32 [R]	≤4 [R]			≥64 [R]	≤4 [R]	≥64 [R]	0.5 [R]
16373940-92	R	16 [R]	≥32 [R]	≤4 [R]			≥64 [R]	≤4 [R]	≥64 [R]	32 [R]
16380461-93	R	16 [R]	≥32 [R]	≤4 [R]			≥64 [R]	≤4 [R]	≥64 [R]	4 [R]
16381897-94	R	≥32 [R]	≥32 [R]	≤4 [R]			≥64 [R]	≤4 [R]	≥64 [R]	8 [R]
16403990-95	R	8 [R]	≥32 [R]	≤4 [R]			≥64 [R]	≤4 [R]	≥64 [R]	8 [R]
16410965-97	R	≥32 [R]	≥32 [R]	≤4 [R]			≥64 [R]	≤4 [R]	≥64 [R]	32 [R]
16412734-98	R	16 [R]	≥32 [R]	≤4 [R]			≥64 [R]	≤4 [R]	≥64 [R]	0.5 [R]
16414518-99	R	≥32 [R]	≥32 [R]	≥128 [R]			≥64 [R]	≤4 [R]	32 [R]	1 [R]
16423798-100	R	4 [R]	≥32 [R]	≤4 [R]			≥64 [R]	≤4 [R]	≥64 [R]	8 [R]
16452179-101	R	4 [R]	≥32 [R]	≤4 [R]			≥64 [R]	≤4 [R]	≥64 [R]	32 [R]
16460854-103	R	4 [R]	≥32 [R]	≤4 [R]			≥64 [R]	≤4 [R]	≥64 [R]	8 [R]
16461348-104	R	8 [R]	≥32 [R]	≤4 [R]			≥64 [R]	≤4 [R]	≥64 [R]	0.5 [R]
16463421-105	R	4 [R]	≥32 [R]	≤4 [R]			≥64 [R]	≤4 [R]	≥64 [R]	8 [R]
16480570-107	R	8 [R]	≥32 [R]	≤4 [R]			≥64 [R]	16 [R]	≥64 [R]	8 [R]
16490102-109	R	≥32 [R]	≥32 [R]	≥128 [R]			≥64 [R]	32 [R]	≥64 [R]	2 [R]
16502100-111	R	8 [R]	≥32 [R]	8 [R]			≥64 [R]	8 [R]	≥64 [R]	32 [R]
16502287-112	R	4 [R]	≥32 [R]	≤4 [R]			≥64 [R]	≤4 [R]	≥64 [R]	8 [R]
16515043-116	R	≥32 [R]	≥32 [R]	≤4 [R]			≥64 [R]	≤4 [S]	≥64 [R]	32 [R]
16523394-117	R	≥32 [R]	≥32 [R]	≤4 [R]			≥64 [R]	16 [R]	≥64 [R]	2 [R]
16080470-121	R	4 [R]	≥32 [R]	≤4 [R]		2 [I]	≥64 [R]	≤4 [S]	≥64 [R]	4 [R]
16101701-122	R	≥32 [R]	≥32 [R]	≥128 [R]		≥64 [R]	≥64 [R]	≤4 [R]	≥64 [R]	16 [R]
16102833-123	R	8 [R]	≥32 [R]	≤4 [R]		4 [I]	≥64 [R]	≤4 [S]	≥64 [R]	≤1 [R]
16110414-124	R	16 [R]	≥32 [R]	≤4 [R]		2 [R]	≥64 [R]	≤4 [R]	≥64 [R]	16 [R]
16120913-125	R	16 [R]	≥32 [R]	8 [R]		2 [R]	≥64 [R]	≤4 [R]	≥64 [R]	4 [R]
16124907-127	R	4 [R]	≥32 [R]	≤4 [R]		2 [R]	≥64 [R]	≤4 [R]	≥64 [R]	16 [R]
16203509-133	R	4 [R]	≥32 [R]	≤4 [R]		2 [R]	≥64 [R]	≤4 [R]	≥64 [R]	4 [R]
16210391-134	R	8 [R]	≥32 [R]	≤4 [R]		2 [R]	≥64 [R]	≤4 [R]	≥64 [R]	4 [R]
16224380-135	R	4 [R]	≥32 [R]	≤4 [R]		≤1 [R]	≥64 [R]	≤4 [R]	8 [R]	4 [R]
16223590-136	R	4 [R]	≥32 [R]	≤4 [R]		≤1 [R]	≥64 [R]	≤4 [R]	16 [R]	4 [R]

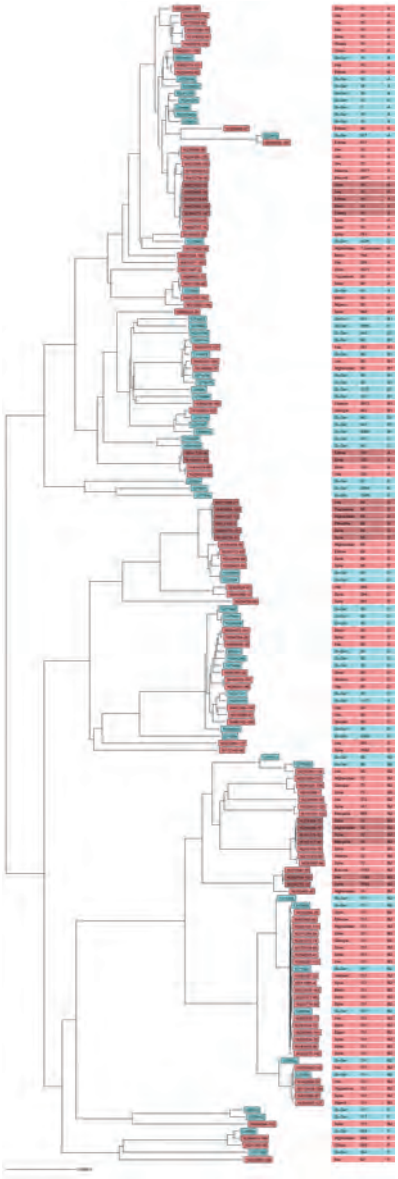
CFTR	GENT	TOBR	TRIM	SXT	NITR	FOSF	CIPR	IMIP	MERO	COL
R	≤1 [S]	≤1 [S]	≤0.5 [S]	≤20 [S]	≤16 [S]		≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320 [R]	≤16 [S]		≥4 [R]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≥16 [R]	≥16 [R]	≥16 [R]	≥320 [R]	≤16 [S]		≥4 [R]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≥16 [R]	4 [R]	≤0.5 [S]	≤20 [S]	≤16 [S]		≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≤0.5 [S]	≤20 [S]	≤16 [S]		≥4 [R]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320 [R]	≤16 [S]		≥4 [R]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≥16 [R]	≤0.5 [S]	≤20 [S]	≤16 [S]		≥4 [R]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≥16 [R]	8 [R]	≤0.5 [S]	≤20 [S]	≤16 [S]		≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≥16 [R]	8 [R]	≤0.5 [S]	≤20 [S]	≤16 [S]		≥4 [R]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≥16 [R]	8 [R]	≤0.5 [S]	≤20 [S]	≤16 [S]		0.5 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≥16 [R]	≤0.5 [S]	≤20 [S]	≤16 [S]		≥4 [R]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≥16 [R]	8 [R]	≥16 [R]	≥320 [R]	≤16 [S]		≥4 [R]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320 [R]	≤16 [S]		≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≤20 [S]	≤16 [S]		≥4 [R]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320 [R]	≤16 [S]		≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320 [R]	≤16 [S]		≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320 [R]	64 [S]		≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≤0.5 [S]	≤20 [S]	≤16 [S]	≤16 [S]	≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≤0.5 [S]	≤20 [S]	≤16 [S]	≤16 [S]	≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320 [R]	≤16 [S]	≤16 [S]	≥4 [R]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≤0.5 [S]	≤20 [S]	≤16 [S]	≤16 [S]	≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≥16 [R]	4 [R]	≤0.5 [S]	≤20 [S]	≤16 [S]	≤16 [S]	≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≤0.5 [S]	≤20 [S]	≤16 [S]	≤16 [S]	≥4 [R]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≥16 [R]	8 [R]	≤0.5 [S]	≤20 [S]	≤16 [S]	≤16 [S]	≥4 [R]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320 [R]	≤16 [S]	≤16 [S]	≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≤0.5 [S]	≤20 [S]	≤16 [S]	≤16 [S]	0.5 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320 [R]	≤16 [S]	≤16 [S]	2 [R]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320 [R]	≤16 [S]	≤16 [S]	≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≤20 [S]	≤16 [S]	≤16 [S]	0.5 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320 [R]	32 [S]	≤16 [S]	≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≤0.5 [S]	≤20 [S]	≤16 [S]	≤16 [S]	0.5 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≤0.5 [S]	≤20[S]	64 [I]	≤16 [S]	≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≥16 [R]	4 [R]	≥16 [R]	≥320 [R]	≤16 [S]	≤16 [S]	0.5 [S]	2 [R]	1 [R]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320 [R]	≤16 [S]	≤16 [S]	≥4 [R]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320 [R]	≤16 [S]	≤16 [S]	≥4 [R]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≥16 [R]	8 [R]	≥16 [R]	≥320 [R]	≤16 [S]	≤16 [S]	0.5 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320 [R]	≤16 [S]	≤16 [S]	≥4 [R]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≤20 [S]	≤16 [S]		≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320 [R]	≤16 [S]		0.5 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320 [R]	≤16[S]		≤0.25 [S]		≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≤20 [S]	≤16 [S]		1 [I]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	8 [R]	≥16 [R]	≥320 [R]	≤16 [S]		≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320 [R]	≤16 [S]		1 [I]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≤0.5 [S]	≤20 [S]	≤16 [S]		≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≥16 [R]	8 [R]	≥16 [R]	≥320 [R]	≤16 [S]		≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≤0.5 [S]	≤20 [S]	≤16 [S]		≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≥16 [R]	8 [R]	≥16 [R]	≥320 [R]	≤16 [S]		≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]

SUPPLEMENTARY TABLE S1. Continued

	MIC (mg/L)									
Isolate	**AMOX**	**AMC**	**AMP**	**PITA**	**CZOL**	**CFEP**	**CFUR**	**CFOX**	**CFOT**	**CFTA**
16253777-137	R	8 [R]	≥32 [R]	≤4 [R]		≤1 [R]	≥64 [R]	≤4 [R]	8 [R]	≤1 [R]
16280325-138	R	≥32 [R]	≥32 [R]	≥128 [R]		≤1 [R]	≥64 [R]	≥64 [R]	8 [R]	≥64 [R]
16293985-141	R	16 [R]	≥32 [R]	≤4 [R]		4 [R]	≥64 [R]	≤4 [R]	≥64 [R]	16 [R]
16303275-142	R	8 [R]	≥32 [R]	≤4 [R]		4 [R]	≥64 [R]	≤4 [R]	≥64 [R]	8 [R]
16313830-144	R	≤2 [R]	≥32 [R]	≤4 [R]		≤1 [R]	≥64 [R]	≤4 [R]	≥64 [R]	≤1 [R]
16354278-145	R	4 [R]	≥32 [R]	≤4 [R]			≥64 [R]	≤4 [R]	≥64 [R]	8 [R]
16364275-147	R	≥32 [R]	≥32 [R]	≤4 [R]			≥64 [R]	≤4 [S]	≥64 [R]	8 [R]
16384420-149	R	≥32 [R]	≥32 [R]	≤4 [R]			≥64 [R]	≥64 [R]	≥64 [R]	32 [R]
16393704-151	R	16 [R]	≥32 [R]	≤4 [R]			≥64 [R]	≤4 [R]	≥64 [R]	8 [R]
16400373-152	R	≤2 [R]	≥32 [R]	≤4 [R]			≥64 [R]	≤4 [R]	≥64 [R]	1 [R]
16404584-153	R	≤2 [R]	≥32 [R]	≤4 [R]			≥64 [R]	≤4 [R]	≥64 [R]	2 [R]
16430618-154	R	8 [R]	≥32 [R]	≤4 [R]			≥64 [R]	≤4 [R]	≥64 [R]	8 [R]
16462411-155	R	4 [R]	≥32 [R]	≤4 [R]			≥64 [R]	≤4 [R]	≥64 [R]	8 [R]
16472571-157	R	16 [R]	≥32 [R]	≤4 [R]			≥64 [R]	≤4 [R]	≥64 [R]	4 [R]
16472092-158	R	≤2 [R]	≥32 [R]	≤4 [R]			≥64 [R]	≤4 [R]	≥64 [R]	16 [R]
16501528-160	R	≥32 [R]	≥32 [R]	≤4 [R]			≥64 [R]	≤4 [R]	≥64 [R]	32 [R]
16504672-161	R	≥32 [R]	≥32 [R]	≤4 [R]			≥64 [R]	32 [R]	≥64 [R]	4 [R]
16512707-162	R	≤2 [R]	≥32 [R]	≤4 [R]			≥64 [R]	≤4 [R]	≥64 [R]	4 [R]
16512879-163	R	≤2 [R]	≥32 [R]	≤4 [R]			≥64 [R]	≤4 [R]	≥64 [R]	4 [R]
16522488-166	R	4 [R]	≥32 [R]	≤4 [R]			≥64 [R]	≤4 [R]	≥64 [R]	8 [R]
16081155-167	R	16 [R]	≥32 [R]	8 [R]	4[R]		≥64 [R]	≤4 [R]	≥64 [R]	16 [R]

Phenotypic resistance of Asylum Seekers group isolates to all main antibiotic agents, routinely tested at Certe laboratory. MIC=minimum inhibitory concentration, AMOX=amoxicillin, AMC=amoxicillin/clavulanic acid, AMP=ampicillin, PITA=piperacillin/tazobactam, CZOL=cefazolin, CFEP=cefepime, CFUR=cefuroxime, CFOX=cefoxitin, CFOT=cefalothin, CFTA=ceftazidime, CFTR=ceftriaxone, GENT=gentamycin, TOBR=tobramycin, TRIM=trimethoprim, SXT=trimethoprim/sulfamethoxazole, NITR=nitrofurantoin, FOSF=fosfomycin, CIPR=ciprofloxacin, IMIP=imipenem, MERO=meropenem, COL=colistin

CFTR	GENT	TOBR	TRIM	SXT	NITR	FOSF	CIPR	IMIP	MERO	COL
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320 [R]	64 [S]		≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	2 [S]	≥16 [R]	≥320 [R]	≤16 [S]		≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≥16 [R]	≥16 [R]	≥320 [R]	≤16 [S]	≤16 [S]	≥4 [R]		≤0.25 [S]	
R	≥16 [R]	8 [R]	≥16 [R]	≥320 [R]	≤16 [S]		≥4 [R]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320 [R]	≤16 [S]		≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320 [R]	≤16 [S]	≤16 [S]	≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320 [R]	≤16 [S]	≤16 [S]	0.5 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≥16 [R]	8 [R]	≥16 [R]	≥320 [R]	≤16 [S]	≤16 [S]	≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≥16 [R]	8 [R]	≥16 [R]	≥320 [R]	≤16 [S]	≤16 [S]	≥4 [R]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320 [R]	≤16 [S]	≤16 [S]	≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≤0.5 [S]	≤20 [S]	≤16 [S]	≤16 [S]	≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≤0.5 [S]	≤20 [S]	≤16 [S]	32 [S]	≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≥16 [R]	8 [R]	≥16 [R]	≥320 [R]	≤16 [S]	≤16 [S]	0.5 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≤0.5 [S]	≤20 [S]	≤16 [S]	≤16 [S]	1 [I]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320 [R]	≤16 [S]	≤16 [S]	0.5 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320 [R]	≤16 [S]	≤16 [S]	≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320 [R]	32 [S]	≤16 [S]	≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≥16 [R]	≥320 [R]	≤16 [S]	≤16 [S]	0.5 [S]	0.5 [S]	0.5 [S]	≤0.5 [S]
R	≥16 [R]	8 [R]	≥16 [R]	≥320 [R]	≤16 [S]	≤16 [S]	≥4 [R]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≤1 [S]	≤1 [S]	≤0.5 [S]	≤20 [S]	≤16 [S]	≤16 [S]	≤0.25 [S]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]
R	≥16 [R]	≥16 [R]	≤0.5 [S]	≤20 [S]	32 [S]		≥4 [R]	≤0.25 [S]	≤0.25 [S]	≤0.5 [S]

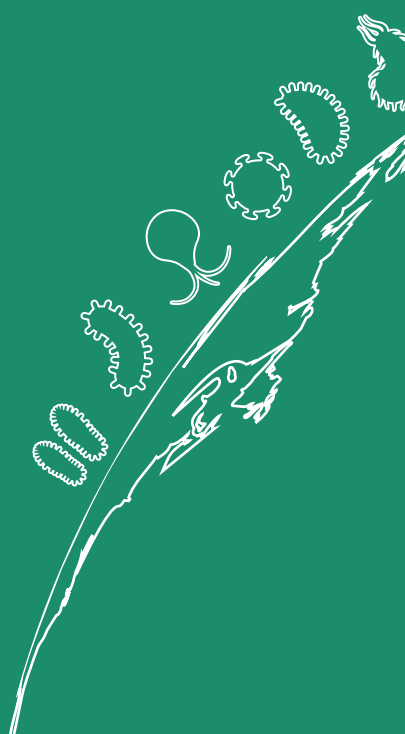


SUPPLEMENTARY FIGURE S1. cgMLST Neighbor Joining Tree including asylum seekers group and control group isolates. The genomes were analyzed using an ad hoc *E. coli* scheme based on 2764 targets including 242851 bp. Control group isolates derived from health institutions near the Dutch-German border region (Du-Ger). Isolates that formed clusters in further phylogenetic analysis are marked with dark pink color. Please note that for imaging purposes, distances between the isolates are not in proportion with the allelic distances. As a result, some isolates may appear as a cluster, but are singletons based on their allelic distances. This figure appears in colour in the online version of JAC and in black and white in the printed version of JAC.

SUPPLEMENTARY FIGURE S2. Minimum spanning tree of the asylum seekers group and control group isolates. The genomes were analyzed using an ad hoc *E. coli* scheme based on 2764 targets. Maximum allelic distance of 10 alleles or less was used to define a cluster. ST of the isolates are shown in the bubbles and allelic distance between isolates is expressed on the lines connecting them. Clusters are labeled and indicated by gray zones around the included isolates.

PART II

Screening and vaccination policies



06

Efficacy of ivermectin mass-drug administration to control scabies in asylum seekers in the Netherlands: A retrospective cohort study between January 2014 – March 2016

PLOS NEGLECTED TROPICAL DISEASES. VOLUME 12, ISSUE 5, E0006401 (2018)

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ABSTRACT

Scabies is a skin infestation with the mite *Sarcoptes scabiei* causing itch and rash and is a major risk factor for bacterial skin infections and severe complications. Here, we evaluated the treatment outcome of 2866 asylum seekers who received (preventive) scabies treatment before and during a scabies intervention programme (SIP) in the main reception centre in the Netherlands between January 2014 and March 2016. A SIP was introduced in the main national reception centre based on frequent observations of scabies and its complications amongst Eritrean and Ethiopian asylum seekers in the Netherlands. On arrival, all asylum seekers from Eritrea or Ethiopia were checked for clinical scabies signs and received ivermectin/permethrin either as prevention or treatment. A retrospective cohort study was conducted to compare the reinfestations and complications of scabies in asylum seekers who entered the Netherlands before and during the intervention and who received ivermectin/permethrin. In total, 2866 asylum seekers received treatment during the study period (January 2014 ± March 2016) of which 1359 (47.4%) had clinical signs of scabies. During the programme, most of the asylum seekers with scabies were already diagnosed on arrival as part of the SIP screening (580 (64.7%) of the 897). Asylum seekers with more than one scabies episode reduced from 42.0% (194/462) before the programme to 27.2% (243/897) during the programme (RR = 0.64, 95% CI = 0.55±0.75). Development of scabies complications later in the asylum procedure reduced from 12.3% (57/462) to 4.6% (41/897). A scabies prevention and treatment programme at start of the asylum procedure was feasible and effective in the Netherlands; patients were diagnosed early and risk of reinfestations and complications reduced. To achieve a further decrease of scabies, implementation of the programme in multiple asylum centres may be needed.

INTRODUCTION

In 2015, several outbreaks of scabies amongst asylum seekers at refugee camps and reception centres in Europe were reported[1–3]. Scabies is an infestation of the skin with the mite *Sarcoptes scabiei*. The mites are transmitted by close and prolonged skin to skin contact. Individuals with a severe form of scabies, such as crusted scabies, may harbour millions of mites and are highly contagious[4]. A manifestation of scabies mostly results in skin burrows, erythematous papules and generalized itching[5]. Secondary infections can lead to life-threatening complications including sepsis[6]. In 2017, the WHO recognized scabies as a neglected tropical disease[7]. Crowded conditions and frequently poor access to health care are major risk factors for scabies outbreaks and most likely gave rise to its recent emergence and spread in refugee camps[8].

Individual patients with uncomplicated scabies can be efficiently treated with permethrin or ivermectin[9]. However, mass outbreaks can be difficult to control and current knowledge on adequate prevention and treatment strategies for scabies in asylum seekers is limited. On a population level, mass drug administration with ivermectin was proven to be efficacious for the control of scabies in a highly endemic population in Fiji[10]. The greatest decline in the number of patients with scabies was seen in the treatment arm with 200ug/kg ivermectin[11]. Mass treatment with ivermectin and intensive active case finding results in long term control of scabies in community settings, but previous studies have not dealt with outbreaks as seen in asylum seekers[11,12].

In the Netherlands, the treating nurses and physicians noticed that asylum seekers originating from Eritrea and Ethiopia were particularly affected by scabies and frequently presented complications related to scabies. For this reason, an intervention programme for scabies was introduced in the national reception centres for asylum seekers in the Netherlands in July 2015.

This study aims to describe the epidemiology of scabies among asylum seekers that arrive in the Netherlands and to evaluate the effectiveness of a scabies intervention programme (SIP). We hypothesize that preventive treatment and early detection of scabies in a high-risk group reduces the number of episodes and the complication rate. Our data may conceivably help to improve the care of asylum seekers with scabies and may be useful to implement screening strategies in other vulnerable populations.

MATERIALS AND METHODS

Ethics statement

This retrospective cohort study was evaluated by the ethics committee and was waived in accordance with Dutch legislation owing to its retrospective nature (University Medical Centre Groningen, METc number 2015/573). No written informed consent was obtained from patients for the use of retrospective data but patient information was anonymized and de-identified prior to analysis.

Asylum seeking procedure in the Netherlands

The number of asylum seekers applications in the Netherlands was 29.790 in 2014, 56.370 in 2015, and 35100 in 2016[13]. Among them, 13% (4056/29790) originated from Eritrea and Ethiopia in 2014, 15.7% (8682/58880) in 2015, and 9.2% (3235/35100) in 2016[13]. The Netherlands operates a centralised system for asylum applications. Asylum seekers start their asylum procedure at one of the three reception centres in the Netherlands; Ter Apel, Budel and Veenhuizen. The majority of asylum seekers present at the reception centre in Ter Apel. Each asylum seeker centre in the Netherlands has its own primary health care centre organised by the national health care service for asylum seekers (GCA).

Within the first three days following arrival, individuals are identified, registered and then screened for active pulmonary tuberculosis. The regional public health services and the primary health care centre of asylum seekers in Ter Apel started an entrant screening programme, called the *'Scabies Intervention Programme'* in July 2015 based on their observations of complicated scabies amongst asylum seekers arriving from Ethiopia and Eritrea.

The scabies intervention programme

The SIP targeted asylum seekers from two countries. Asylum seekers from Eritrea and Ethiopia were selected based on the high prevalence of scabies observed among asylum seekers from these countries. Only the asylum seekers from these two countries were actively screened and were treated or given ivermectin/permethrin preventive treatment. It was practically not feasible to screen and treat all asylum seekers independent of their country of origin. In the first two days after arrival all asylum seekers from Eritrea and Ethiopia received information about scabies and its treatment with the help of a video in Tigrinya. Next their clothes were washed, they received temporary clothes, and were examined by a nurse for skin lesions. The nurses involved in the SIP worked at the health care centre which

is based at the asylum centre. They gained experience during the earlier scabies outbreaks. This experience was complemented by training by the attending general practitioner based on a protocol developed by the National Institute of Public Health and the Environment[14]. The protocol advices on standard examination of the limbs. If skin abnormalities were observed on these body parts, a full body examination was performed if approved by the asylum seeker. Hand lenses were available, but not frequently used. During the intervention, the nurses would consult the attending physician if in doubt and the physician could refer the patient to a dermatologist if needed.

Asylum seekers with skin lesions or complaints compatible with scabies were treated with ivermectin at diagnosis and were invited to return to the health centre two weeks later in order to receive a second dose of ivermectin. Asylum seekers with complicated scabies or other skin diseases were referred to the general practitioner at the primary health care centre Ter Apel for immediate medical evaluation. All asylum seekers without a contraindication received ivermectin (0.2mg/kg, p.o.) under direct supervision of the nurse during the same visit. If ivermectin was contraindicated, for example in pregnant women and in children under the age of one, topical treatment with permethrin was given. All asylum seekers from Eritrea or Ethiopia without clinical signs and symptoms of scabies received a single dose of ivermectin. They travelled and arrived together and were considered to be contacts of the asylum seekers having scabies.

Selection of participants

A retrospective cohort study was conducted at the primary health care centre located in the national reception centre for asylum seekers. The pharmacy records from the main reception center Ter Apel were used to identify all asylum seekers who received ivermectin/permethrin to treat or prevent scabies based on contact tracing between “January 1st 2014 and March 14th 2016. The medical records of these asylum seekers were followed over time (15–36 months) to check for alternative diagnoses and repeated use of ivermectin/permethrin. Medical records of asylum seekers are electronical patient files and can be accessed by health care workers in any asylum centre in the Netherlands after transfer of the asylum seeker. Data from asylum seekers were excluded from analysis if the pharmacy records in Ter Apel indicated use of ivermectin/permethrin without any mentioning of these medications or the diagnosis scabies in the medical file. The extraction of the

ivermectin/permethrin prescriptions from the pharmacy record was independent of the country of origin of the asylum seeker. This data collection remained the same before and after introduction of the SIP.

Data on demographic characteristics; comorbidities; clinical scabies manifestations including complications; lab results (e.g. culture results from secondary infected lesions), and treatment for scabies as given in the intervention programme and the standard care (ivermectin, permethrin or both) have been extracted from medical records.

Scabies was defined as complicated if a patient had to be referred to the hospital, was treated for secondary infections, needed wound care, or received antibiotics for scabies complications. Rash and itch after scabies treatment may persist after successful treatment[9]. Complaints or symptoms of scabies within two weeks of treatment were therefore counted as part of the same episode.

Statistical analysis

IBM SPSS Statistics for Windows, Version 23.0 was used to collect and analyse the data. Descriptive statistics were used for characteristics of all patients who visited the health care centre and registered as having scabies. A Relative Risk (CI) was calculated for the reinfestations before and during the SIP. The number of days until first scabies manifestation before and after the SIP was compared and calculated by Mann-Whitney-U.

RESULTS

Study population and general characteristics

During the study period, 3201 asylum seekers received ivermectin/permethrin at least once. Out of these asylum seekers, 2866 (89.5%) had a medical record with sufficient information to be included for further analysis (Figure 1). Asylum seekers who needed scabies treatment or prophylaxis before introduction of the SIP mainly originated from Ethiopia and Eritrea. The majority was male, and the mean (sd) age was 24 (± 9) years. Comorbidities were reported among 32 asylum seekers before SIP, and among 49 asylum seekers after the SIP. Comorbidities included tuberculosis (n = 47), hepatitis B/C (n = 14), HIV (n = 14), and diabetes (n = 7). There was no difference in the distribution of comorbidities before and after the SIP.

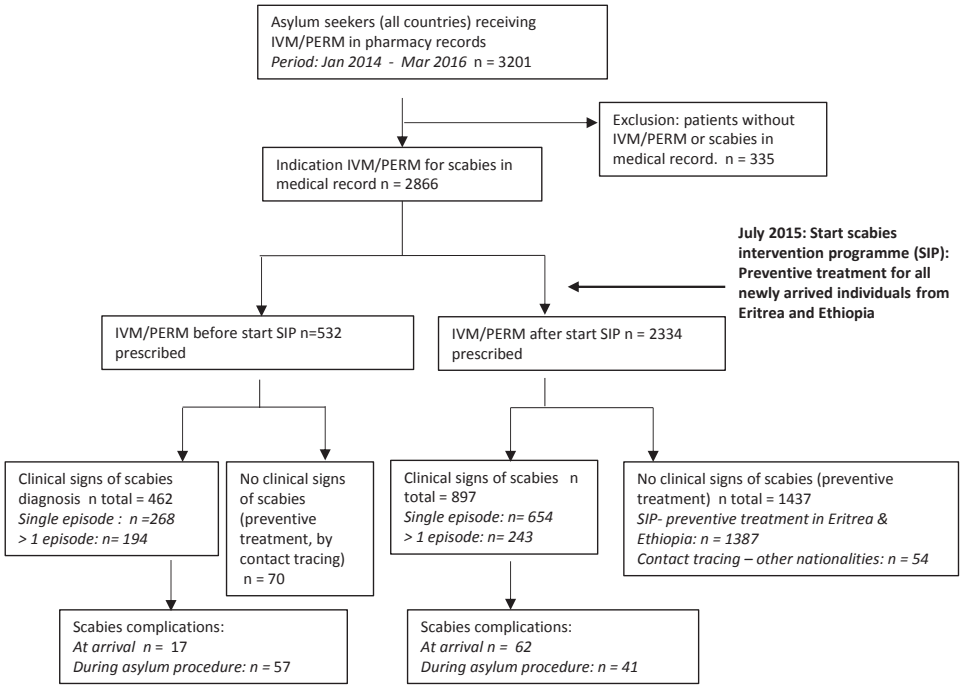

FIGURE 1. Flow chart of study participants January 2014-March 2016, *IVM/PERM = ivermectin/permethrin.

The indication for the use of ivermectin/permethrin in 2866 asylum seekers is summarized in Table 1. During the SIP, 580 (64.7%) of the 897 asylum seekers with signs and symptoms of scabies were identified through the scabies programme on arrival in the Netherlands and received treatment at the reception centre on the first day of arrival. The other 317 (35.3%) asylum seekers received their first treatment at one of the asylum health centres across the Netherlands after a median (IQR) of 83.5 days (46.8–178.8) after arrival.

Clinical manifestations and diagnosis of scabies

An overview of the clinical manifestations at the first episode of the 1359 scabies patients is given in Table 2. 33.5% of the asylum seekers presented with more than one sign or symptom of scabies. Itch was reported in 77% of the episodes. Other signs or symptoms include burrows and other visible skin defects such as excoriations. Episodes with atypical presentations of scabies in the face (n = 17) and neck (n = 13) were noticed in combination with lesions on the hand and in the genital area (Figure2).

TABLE 1. Indication for treatment in the study population before and after start of the SIP by gender and country of origin (total n = 2866)

	Preventive treatment only (SIP/ contact tracing[1])	Single treatment for clinical scabies signs/symptoms	> 1 episodes with clinical signs/ symptoms scabies	Developed scabies despite earlier preventive treatment[2]	Total
Before SIP (n = 532)					
Male (%)	61.4	76.6	90.7	83.3	79.9
Country of origin (n)					
Eritrea	55	137	136	13	341
Ethiopia	13	95	44	4	156
Other Africa	0	14	2	1	17
Other; Eastern Europe & South America (%)	0	0	1	0	1
Other; Middle East & South Asia (%).	2	9	5	0	16
Missing	0	1	0	0	1
TOTAL	**70**	**256**	**188**	**18[2]**	**531**
After initiation of the SIP (n = 2334)					
Male (%)	54.3	75.9	81.1	65.8	62.3
Country of origin (n)					
Eritrea	644	183	67	128	1022
Ethiopia	745	260	91	135	1231
Other Africa	33	8	4	4	49
Other; Eastern Europe & South America (%)	5	1	1	1	8
Other; Middle East & South Asia (%)	10	9	4	1	24
TOTAL	**1437**	**461**	**167**	**269[2]**	**2334**

[1]Before the start of the SIP all preventive treatments were based on contact tracing. During the SIP contact tracing continued as part of standard care. All individuals from Eritrea and Ethiopia without signs or symptoms of scabies received preventive treatment on arrival.

[2]Respectively 6 and 76 before and during SIP developed multiple scabies episodes despite preventive treatment. These patients are counted in this column only.

TABLE 2. Clinical presentation of scabies and complications before and after start of the programme

Clinical presentation	Before SIP n = **462** n (%)	During SIP n = **897** n (%)	Total n = **1359** n (%)
Itch	371 (80.3)	679 (75.7)	1050 (77.3)
Burrows	49 (10.6)	78 (8.7)	127 (9.3)
Other visible skin defects	161 (34.8)	282 (31.4)	443 (32.6)
Secondary infections	62 (13.4)	87 (9.7)	149 (11.0)
Crusted scabies	3 (0.006)	8 (0.009)	11 (0.009)
Missing in medical record	190	377	567
Complications related to scabies			
Reported or diagnosed on arrival	17 (3.7)	62 (6.9)	79 (5.8)
Reported during asylum procedure	57 (12.3)	41 (4.6)	98 (7.2)

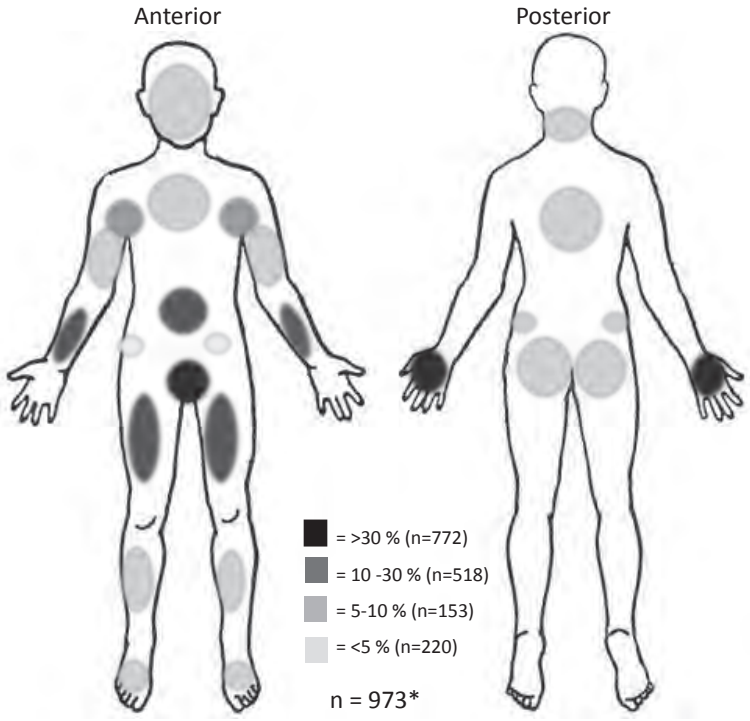

FIGURE 2. Density map of the distribution of scabies signs and symptoms at different body parts.
** Locations of scabies signs were missing in medical records for 386 patients*

Of the 462 asylum seekers with signs and symptoms of scabies before start of the SIP, 12.3% presented with complications of scabies during their asylum procedure, compared to 4.6% of the 897 asylum seekers with signs of scabies after the start of the SIP (RR = 0.37, 95% CI = 0.25–0.54). Asylum seekers with complications presented after a median (IQR) of 6.0 (1–28) days after arrival before start of the SIP and 0 (0–32) days during the SIP (U = 2863.5, p = 0.005).

None of the asylum seekers with skin problems interpreted as being scabies, proved to have an alternative diagnosis during follow up. Before start of SIP, only 13 asylum seekers were initially misdiagnosed and were diagnosed with scabies at their second visit.

Treatment

As described in the previous section, 1359 scabies patients received treatment for the clinical manifestations at the first disease episode. Ivermectin was given 1232 times and permethrin was given 105 times. Twenty-two patients (not during the SIP) received a combined treatment with ivermectin and permethrin due to the disease severity. The protocol included a second dose of treatment after two weeks for the asylum seekers that presented with clinical signs and symptoms of scabies. Among them, 34% (461/1359) had a notification of the intake of a second dose of treatment in their medical record. Scabies reinfestations were more common among individuals reporting the intake of a single dose of ivermectin 40.0% (286/717) compared to the individuals that report the intake of a second dose of ivermectin 27.3% (175/642) (RR = 1.37 95% CI (1.20–1.57).

Antibiotics were prescribed in 117 (68.5%) of the 149 asylum seekers with secondary infections. Most frequently prescribed antibiotics were flucloxacillin (55), amoxicillin/clavulanic acid (29), and fusidic acid (29). Incision and drainage of abscesses were performed in 35 patients. Wound care was needed in 85 patients. Cultures were performed in 12 asylum seekers with secondary infections at the health care centre of the national reception centre. Cultures showed Methicillin-Sensitive Staphylococcus aureus (MSSA) in 9 patients and Methicillin-Resistant Staphylococcus aureus (MRSA) in 3 patients.

Reinfestations

Reinfestations were more common amongst scabies patients before introduction of SIP. During the SIP, 27.2% (243/897) of the scabies patients had more than one disease episode versus 44% (194/462) of the scabies patients before start of the SIP (RR = 0.64, 95% CI = 0.55–0.75).

In total 1691 asylum seekers received preventive treatment on arrival, of which 269 (15.9%) asylum seekers were diagnosed with scabies later in their asylum procedure (after a median (IQR) days of 75 (44–146)). The majority (242 of the 269 (90.0%)) reported during their stay in asylum health centres other than the national receptions centres Ter Apel and Budel. There was no proactive scabies programme in these asylum centres.

DISCUSSION

Frequent observations of scabies and its complications were reported amongst Eritrean and Ethiopian asylum seekers arriving in the Netherlands. Introduction of a scabies prevention and treatment programme on arrival was feasible and resulted in early detection of asylum seekers with scabies. Itch and burrows were the most common clinical manifestations. Atypical scabies presentations in the face and neck were also noticed. The number of scabies reinfestations after treatment and the number of complicated forms of scabies reduced after introduction of the programme. Asylum seekers who received ivermectin/permethrin on arrival but developed scabies in other asylum centres across the Netherlands, presented after a median of 2.5 months after arrival.

Introduction of the SIP was effective in the prevention of scabies outbreaks. Given the high number of the asylum applications in 2014 and 2015[13] a target group for the intervention was selected. The few scabies manifestations amongst asylum seekers from countries other than Ethiopia and Eritrea suggests that the target group of the SIP was well chosen.

Reinfestations after scabies treatment were common before the programme started. After introduction, the number of scabies episodes per person reduced significantly. Prompt treatment of new cases is important for successful scabies control in institutional settings[15,16]. In other institutional settings, a public jail and a hospital ward, collective treatment of persons with oral ivermectin in both a treatment and prophylaxis setting appeared to be effective in the treatment of scabies[17,18]. In

our study, newly developed scabies episodes were mainly seen in asylum health centres other than the national reception centres Ter Apel and Budel. These centres did not have a scabies prevention and treatment programme. This indicates that to achieve a further decrease of scabies, implementation of the programme in multiple asylum centres may be needed.

Definitive diagnosis of scabies relies on microscopic identification of the mites or eggs[19]. However, scabies diagnosis based on clinical recognition by well-trained nurses seemed efficient in this setting with high pre-test probability of having scabies if asylum seekers had itching or typical skin lesion; no scabies patients received alternative diagnoses during follow-up. Diagnostic accuracy of scabies diagnosis based on the combination of symptoms and signs recognition was also proven in a study performed in Mali and Senegal[20]. Over diagnosis of scabies during the SIP could be a factor that contributed to the reduced reinfestations since start of the SIP, but the data collected in this setting with a high pre-test probability of scabies suggests a good positive predictive value.

Secondary infections and complications are common amongst scabies patients[21]. Introduction of the programme reduced the number and the severity of the complicated forms of scabies. It has been suggested that scabies mites provide favourable conditions for onset of S. aureus co-infection[22]. Severe forms of scabies such as bacterial super infections and crusted scabies were reported in this study. Culture of the secondary infections tested positive for both the presence of MSSA and MRSA. However, the number of coinfections is relatively low compared to other studies that describe secondary infections related to scabies[23].

A limitation of this study is the unknown duration of stay of the asylum seekers in the asylum centers. Therefore, it is impossible to calculate the exact incidence rate of scabies. Due to the frequent relocations of asylum seekers to other asylum centers within the Netherlands without a proactive scabies programme, reinfestations may occur by contact with untreated contagious individuals. Scabies manifestations after preventive treatment occurred after a minimum time period of two and a half months, suggesting that initial preventive treatment was effective. Other factors may have led to a reduction in the rate of reinfestations which are not included in this study, e.g. improved housing of asylum seekers. However, we are unaware of such changes in policy that could lead to a reduction in the rate of reinfestations.

Finally, participation in the SIP was on a voluntary basis. The number of patients that refused participation in the programme is unknown and these individuals could

influence the efficacy of the programme. However, health care workers did not observe asylum seekers who refused participation which suggests that refusal rate was low.

Controlling scabies amongst asylum seekers is important to reduce the risk of complicated cases and to prevent the spread of scabies amongst asylum seekers at asylum centres in the Netherlands. The centralized health care system for asylum seekers that is used in the Netherlands allows accurate follow up of asylum seekers and provides unique retrospective data on the programme.

The systematic examination of the skin by nurses as part of this programme also results in early identification of other skin diseases such as chronic wounds, cutaneous leishmaniasis and eczema and leads to referral to the general practitioner in case of other systemic signs like fever. This programme therefore has the potential for an integrated control of skin conditions and human-to-human transmittable diseases, such as louse borne relapsing fever[24]. To our knowledge this is the first study to investigate the effect of a screening and mass-drug administration programme for scabies control in asylum seekers. The programme helped to be up to scratch with itchy outbreaks by early detection and reducing the number of reinfestations and complications.

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07

Correspondence: The public health control of scabies: priorities for research and action.

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We read the Article by David Engelman and colleagues[1] with interest. Their overview of the key operational research questions to develop a global control programme for scabies provides a clear research agenda for the years to come[1]. Mass drug administration (MDA) using ivermectin reduced the prevalence of both scabies and impetigo tremendously in Fiji with a sustained effect even 24 months after the intervention[2]. Future studies should prioritise the inclusion of non-island populations.

Outbreaks of scabies occur in refugee camps and centres worldwide. We want to emphasise the need for evidence supporting MDA to prevent and treat outbreaks among refugees. Scabies burden is high among refugees, with an increased rate of complications including secondary infections[3]. Standard care based on topical permethrin of people with scabies and their contacts is unlikely to contain outbreaks if based on passive case detection considering the inadequate access to health care among refugees. In high-income countries, ivermectin-based MDA could be integrated into screening programmes and might contribute to the reciprocity of the overall programme by immediately relieving suffering[4]. Retrospective data provided evidence supporting ivermectin-based MDA by early detection and treatment, reducing the number of reinfestations and complications even after asylum seekers' transfer to other centres[5]. Prospective data are needed to increase the level of evidence, determine the scabies prevalence justifying MDA, and to decide on the optimal MDA interval, which might depend on the number of newly arriving refugees. Moxidectin or slow-release ivermectin might provide added value in this setting to control scabies.

We declare no competing interests.

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08

National approaches to the vaccination of recently arrived migrants in Europe: A comparative policy analysis across 32 European countries

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ABSTRACT

Background

Migrants may be underimmunised and at higher risk of vaccine-preventable diseases, yet there has been no comprehensive examination of what policies are currently implemented across Europe targeting child and adult migrants. We analysed vaccination policies for migrants in 32 EU/EEA countries and Switzerland.

Materials and Methods

Using framework analysis, we did a comparative analysis of national policies and guidelines pertaining to vaccination in recently arrived migrants through a systematic guideline and literature review and by approaching national experts.

Results

Six (18.8%) of 32 countries had comprehensive policies specific to the vaccination of migrants (two focused only on child migrants, four on both adults and children). Nineteen (59.4%) countries applied their national vaccination schedule for migrant vaccinations, predominantly focusing on children; and five (15.6%) countries had circulated additional migrant-specific resources to relevant health-care providers. In six (18.8%) countries, policies on migrant vaccination focused on outbreak-specific vaccines only. In ten (31.3%) countries, policies focused on priority vaccinations, with polio being the vaccine most commonly administered and heterogeneity noted in vaccines recommended to adults, adolescents, and children. Eighteen (56.3%) countries recommended that an individual should be considered as unvaccinated where vaccination records were missing, and vaccines re-administered. Nine (28.1%) countries reported that specific vaccinations were mandatory.

Conclusion

There is considerable variation in policies across Europe regarding approaches to vaccination in adult and child migrants, and a lack of clarity on optimum ways forward, what vaccines to offer, with a need for robust research in this area. More emphasis must be placed on ensuring migrant-specific guidance is disseminated to front-line healthcare professionals to improve vaccine delivery and uptake in diverse migration populations across the region.

INTRODUCTION

Migrants within the European Union (EU) may represent an underimmunised group, with implications for outbreaks of vaccine-preventable diseases[1]. Outbreaks of measles and hepatitis A have been documented in migrant populations in Europe[2,3], and diseases including poliomyelitis remain endemic in some migrant sending countries[4]. Migrants in the EU and European Economic Area (EEA) are a diverse group, including both internal EU migrants – moving from one country in Europe to another – and external non-EU migrants. Although the role of migrants in epidemics of vaccine-preventable diseases is unclear, mainly due to poor data collection in this area, the current multi-country measles epidemic in the EU/EEA has involved EU migrants moving from and between countries with large epidemics[5]. Large numbers of recently arrived migrants to the EU may have an uncertain vaccination status, including incomplete vaccination history and/or missing documentation of previous vaccinations, with implications for health-care providers and how to approach catch-up vaccination[6]. In a cohort of 2126 asylum-seeking children to Denmark 30% were considered not to be immunised in accordance with the Danish schedule, with underimmunisation particularly high in adolescent migrants (aged 10–17 years)[7]. Strategies and approaches to engaging migrant populations in vaccination are not clear due to the lack of high quality studies assessing vaccination implementation[8].

A recent report has highlighted wide disparities in access to healthcare and vaccination across Europe, with undocumented (irregular migrants) in particular unable to access free vaccination because of administrative barriers and lack of entitlement to free health services including vaccination services[9]. This is despite the fact that ensuring high levels of coverage is a key priority of the European Vaccine Action Plan[10], in which all countries have committed to eliminating endemic measles and rubella (> 95% coverage with the measles mumps rubella vaccine), controlling hepatitis B infection, and sustaining polio free status. Innovations in service provision to ensure hard-to-reach groups, including migrants, access vaccination services remains an important component to reducing vaccine-preventable diseases in Europe.

However, current approaches to the vaccination of migrants have not been well documented to date, and it is acknowledged that there are additional challenges in ensuring equitable access to vaccines in diverse and mobile migrant populations[9,11]. The ongoing refugee crisis has facilitated renewed dialogue around approaches to the screening and vaccination of recently arrived migrants for infectious diseases. The World Health Organization (WHO), United Nations High Commissioner for

Refugees, and the United Nations Children's Fund recommended in 2015 that migrants in the WHO European Region should be vaccinated soon after arrival in accordance with the immunisation schedule of the receiving country in which they intend to stay for more than a week[11], and the European Centre for Disease Prevention and Control (ECDC) is currently developing guidance on approaches to vaccinepreventable diseases in newly arrived migrants[12]. However, there has to date been no comprehensive examination of what policies or guidelines are currently implemented across Europe, or how they compare across countries. In order to facilitate the harmonisation of vaccination policies across Europe and identify best practice, a clear understanding of the different policies and of the key gaps or inconsistencies in such policies is needed[13,14]. We therefore did a comparative analysis of policies and guidelines in EU/EEA countries and Switzerland relating to the provision of vaccinations to recently arrived migrants to identify common approached.

MATERIALS AND METHODS

We documented and analysed vaccination policies for migrants in 32 EU/EEA countries, and Switzerland. The policy analysis was guided by Bardach's health policy framework[15,16], and consisted of a comparative analysis of policies or guidance for vaccination in migrants across European countries. Primary and secondary data sources were used to identify evidence for the analysis. Key migrant groups included recently arrived migrants (foreign born, in the host country < 10 years), refugees (granted asylum), asylum seekers (awaiting a decision on their asylum application in the host country), and undocumented migrants (without necessary authorisation or documents required under host country's immigration regulations). Primary data were obtained through contacting national experts in each country, who were asked to provide both relevant health policy documents. Secondary data consisted of relevant health policy documents and guidelines around vaccination in migrants, which were obtained through a systematic search of the literature and published papers from relevant health bodies such as Ministries of Health.

Approaching national experts

National experts for the included EU/EEA countries and Switzerland were identified through the network of the European Study Group for Infections in Travellers and Migrants (ESGITM), which contributes to activities in the field of travel and migration related infectious diseases as part of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID). Experts were also identified through relevant

publications and key meetings over the last 5 years (e.g. the European Congress of Clinical Microbiology and Infectious Diseases [ECCMID]). Between December 2016 and May 2017, we emailed experts in the following 32 countries: Austria, Belgium, Bulgaria, Cyprus, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland and the United Kingdom (UK). National experts were asked to provide documents relating to national policies or guidelines on vaccination in migrants, with a key focus on national guidelines and definitions, mandatory vaccinations, outbreak specific guidance, priority vaccinations, and incomplete vaccination records. Non-respondents were contacted either by e-mail or phone twice in an effort to include all 32 countries. Where documents were provided in a language other than English, they were translated as needed.

Secondary data collection and analysis

Expert input was complemented by the identification of secondary data on health policies or guidelines across European countries through a systematic search of the literature. First, we searched PubMed and Google Scholar using terms relevant to migrants and vaccinations, including “vaccination”, “immunisation”, “vaccine preventable diseases”, “immunisation”, “migrants”, “refugees”, “European Union”, and “health policy” between inception and June 20, 2017. Additional literature reporting policies or guidance on vaccination in migrants was also identified through internet searches using relevant terms for each specific country, and hand searching through health policy documents and relevant national policy websites (e.g. for Ministries of Health).

Data analysis

Once the relevant data sources had been collated, we utilised framework analysis to synthesise relevant content on policies or guidance for vaccination in migrants across the included countries. Our policy analysis framework focused on key topics including national guidelines and definitions, mandatory vaccinations, outbreak specific guidance, priority vaccinations, and catch-up vaccination in the absence of complete vaccination records. Relevant policies or guidance were extracted and analysed for each country for each of the key framework themes.

RESULTS

National guidelines and definitions

We identified guidance and policy documents for all 32 countries through our database, internet, and hand searches and received responses from experts in 30 EU/EEA countries regarding national or regional guidelines on vaccination in migrants. Using this two-pronged approach, we therefore collated policies and guidance from all 32 countries under study.

We identified significant variation in policies and guidelines for vaccination in migrants across the EU/EEA (Table 1). Six (18.8%) of 32 countries had specific vaccination guidelines for migrants, two of which applied only to child migrants and four to both child and adult migrants; we found that some of these guidelines were very comprehensive in terms of approaches to catch-up vaccination in adults and child migrants, and other were not. Five (15.6%) of 32 countries had circulated migrant-specific resources to relevant health-care providers. 19 (59.4%) of 32 countries apply their national vaccination plan for vaccination in migrants, and two (6.3%) countries used the International Organization for Migration (IOM) handbook with recommendations for vaccination in migrants[17].

TABLE 1. Policy and guidance on vaccination in migrants in EU/EEA countries

Policy/guidance on vaccination in migrants	Number of countries [n=32] (%)
Specific national policy/guidance for migrant vaccination	6 (18.8%) (2 for child migrants only; 4 for adult and child migrants)
Migrant-specific resources are available for healthcare workers; but no national policy/guidelines	5 (15.6%)
National vaccination plan is used and/or "catch up" vaccination document is circulated	19 (59.4%)
IOM handbook[17]	2 (6.3%)

Administration of vaccinations to adults, adolescents, and children

There was considerable heterogeneity across countries regarding which vaccines should be administered to adults and child migrants. Ten (31.3%) countries in total had national guidance or which stated that specific vaccinations should be prioritised for migrants (Figure 1). Polio was the most frequently reported priority vaccine given

to recently arrived migrants, but vaccination for hepatitis B – for example – was not being considered. Figure 1 highlights that there was considerable heterogeneity between what vaccines are recommended to adult, adolescent, and child migrants.

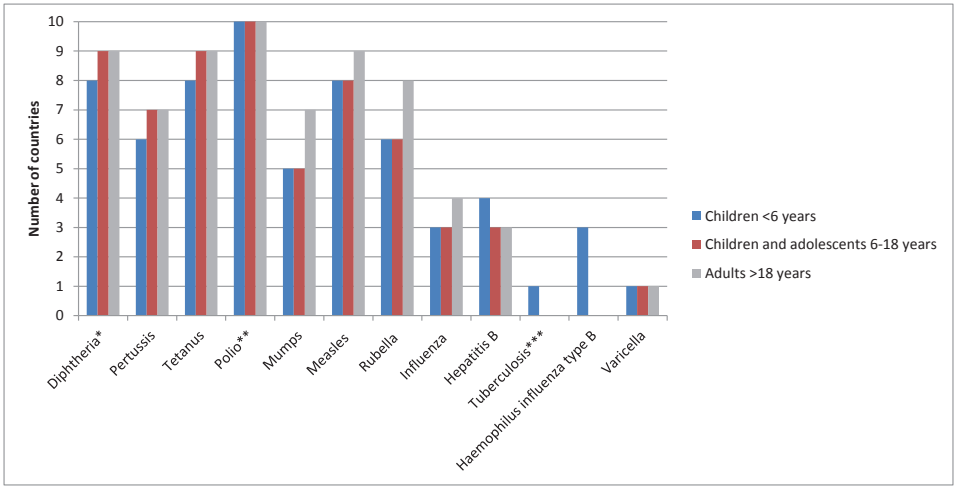

FIGURE 1. Priority vaccines across EU/EEA countries for migrant children, adolescents, and adults in those countries reporting migrant-specific policies.
** In adults, recommendation for pregnant women only*
*** For all people from at-risk countries only*
**** only for newborn babies*

Outbreak-specific recommendations

Six (18.8%) countries reported having specific guidelines or policies in place regarding outbreak-specific vaccinations for migrants. These guidelines differed in content, but in general provided information to health-care providers in recognising certain infectious or epidemic diseases and a name to contact in case of an outbreak among refugees/ migrants. One country recommended meningococcal vaccination when an outbreak is identified through the Ministry of Health's surveillance system[18,19]. In another country, a mobile medical team is responsible in certain areas for administering immunisations to adult migrants who have not been vaccinated in the case of an infectious disease outbreak[20].

Uncertain vaccination status

In 18 (56.3%) of 32 countries policies, guidelines, and/or resources stated that a person should be considered as unvaccinated where vaccination records are missing. In five countries a catch-up immunisation document was available to guide vaccination in migrants with missed vaccinations or a lack of records[20–24]. However, the approach to determine vaccination status varied across countries. For example, oral reporting of vaccination in children was not accepted as proof of vaccination status in most countries. In one country oral reporting of vaccination status was considered to be sufficient, and where there was uncertainty about the vaccination status children are then considered unvaccinated[25,26]. In another country, children below 5 years of age for whom vaccination records were lacking, are assumed to be unvaccinated and subsequently included in the childhood vaccination programme using vaccination intervals based on the age of the child. In this same country for children aged 5–17 years, DTaP-IPV/Hib primary vaccine (DiTeKiPol/Act-Hib) is administered once then antibodies against diphtheria and tetanus are measured 1 month later[27]. Specific guidance exists regarding incomplete vaccinations for migrants from the top three migrant-sending countries at the current time (Syria, Iraq, and Afghanistan) where vaccination coverage was relatively high prior to conflict but has since dropped[28]. This guidance recommends catch-up vaccination in children born since conflicts began in these countries, with reference to the likelihood that vaccination status may also be incomplete in adults arriving from these countries and for whom catch-up vaccination should also be considered[28]. For most countries, there is no specific guidance available on how to approach catch-up vaccination in adult migrants of uncertain vaccination status, but information on priority vaccines in adult migrants was available for 10 countries (Figure 1).

Serology testing prior to vaccination

Four (12.5%) countries recommend against serology testing prior to vaccination for migrants with incomplete vaccinations or a lack of documentation on previous vaccination[22,24–31]. The main reasons noted in the guidance against serology testing included: that the interpretation of serology tests is difficult (3 countries), serology is expensive (2 countries), false negative results often occur (1 country), and that migrants can easily and safely be revaccinated (1 country). Two (6.3%) countries, however, do recommend serology testing prior to vaccination. For example, the guideline recommends hepatitis B serology testing at the health check on arrival to the country, performed as part of screening for these infectious diseases[32]. Another

country recommended the approach that all migrant women of childbearing age without a history of varicella infection should have their immunity checked, and that women with negative serology should be vaccinated[33].

Mandatory vaccination

We found considerable variations across EU/EEA countries in relation to whether vaccinations were mandatory or voluntary for migrants, with nine (28.1%) countries reporting that specific vaccinations were mandatory according to national policy. The definition and regulation of 'mandatory' vaccination policies were not well described, nor were consequences if vaccinations were refused. In most countries, guidelines did not stipulate that vaccinations were mandatory, though they were considered highly recommended.

DISCUSSION

Summary of key findings

There were striking variations in terms of policy and guidance regarding vaccination in migrants across EU/EEA countries, with six (18.8%) of 32 countries having comprehensive policies specific to the vaccination of migrants, of which 2 focused only on child migrants. More than half of the countries applied their national vaccination schedule for migrant vaccinations, which is a response advocated by WHO and others[13]. In ten (31.3%) countries, policies focused on priority vaccinations, with polio being the vaccine most commonly administered and heterogeneity in which vaccines were recommended to adults, adolescents, and children. Some countries reported migrant specific guidelines relating to outbreak-specific vaccine-preventable diseases only, and substantial variation was found across countries relating to whether vaccinations were mandatory. Our analysis found differences across countries when migrant presented to a health service with a missing or incomplete vaccination record, a common phenomenon in this group, with eighteen (56.3%) countries recommending that an individual should be considered as unvaccinated where vaccination records were missing, and vaccines re-administered.

Strengths and limitations

We aimed to provide a comprehensive examination of policies and guidance on the vaccination of recently arrived migrants in EU/EEA countries and Switzerland. Whilst we aimed to systematically search the secondary literature as well as contact

national experts in this field in each European country, the field of vaccination among migrants is moving quickly and policies and guidelines are dependent on political context. Our policy, guideline, and literature search was done up to May 2017, and we are aware that more guidelines could have been published and circulated since this date; however, we have been in dialogue with vaccination experts since May 2017 and are not aware of anything significant that has been published and that would change our overall key findings. There are also numerous regional or local level policies or guidelines that may be implemented across Europe, as well as unpublished documents, which were not identified through our research.

Policy versus practice

It is not clear to what extent these policies, guidelines, and circulated resources were implemented in practice. In a recent EU-EEA-wide questionnaire survey, we found that implementation is considered by experts to be poor, with few initiatives targeting migrants specifically, and that adult migrants may be particularly excluded from catch-up vaccination on or after arrival[34]. This survey also highlighted a lack of clarity around what vaccinations should be given to adult and child migrants. These shortfalls have been reported by others, noting that high quality studies assessing vaccination implementation in migrant populations are lacking with which to inform policy making in this area[8].

Current shortfalls and next steps

The lack of national guidance around provision of basic care to recently arrived migrants has been previously reported[11], and it is well known that approaches to screening for infectious diseases in migrants varies considerably across the EU/EEA[35]. Migrants, we know, face multiple barriers to accessing healthcare on arrival to a host country, including vaccinations. It may be that there is a need for harmonisation of migrant vaccination approaches across European transit and receiving countries, guided by existing recommendations such as those produced by the IOM and others[11,17,36–38], involving non-governmental organizations and statutory service providers, and including some mechanism for monitoring and recording the delivery and uptake of vaccines to migrants specifically. This was highlighted by the European Parliament in January 2016, who called for health policies and health systems in the WHO European Region to better acknowledge migrants[38]. In light of increasingly restrictive health policies across Europe[39] vaccinations must be provided free of charge to high-risk groups, which aligns with European and

international recognition of migrants' rights to health[40]. There are clear clinical, public health, and human rights arguments for promoting access to an acceptable level of free health care, including vaccination, to migrants.

We report that vaccinations were mandatory for migrants in eight (26.7%) countries, a finding supported by data from the Vaccine European New Integrated Collaborative Effort (the VENICE project) – initiated to improve and monitor vaccination programmes in Europe[41]. VENICE data shows that compliance to vaccination programmes in European countries without mandatory vaccination is high among migrants and non-migrants[41], and they question to what extent vaccinations should be mandatory, suggesting that this is an area that needs warrants further discussion. There are numerous reasons migrants may wish not to be vaccinated e.g. cultural beliefs and legal reasons, such as seeking to avoid registration in a country which may require them to claim asylum in that country[13] as well as significant barriers to accessing care, and more robust research is needed to elucidate the key concerns of migrants around vaccination uptake on arrival to an EU/EEA country.

The ECDC vaccine schedule database allows comparison of vaccination policies between countries, highlighting immunisation schedules in all EU countries[42], but the database does not have data on vaccine schedules for migrants specifically. More emphasis must be placed on improving data collection around vaccine-preventable diseases in migrants in the EU/EEA, to better understand the extent to which these groups are both underimmunised and involved in outbreaks, so that targeted programmes can be implemented in relevant groups. The priority vaccines reported in guidelines in this policy analysis reflect current ECDC recommendations that vaccinations be offered according to national immunisation guidelines, with priority given to easily transmitted and/or serious infectious diseases such as polio[37]. The Canadian evidence-based guidelines on the vaccination of newly arrived migrants is more extensive – and covers both adult and child migrants – giving priority to MMR, DTP, polio, varicella, hepatitis B and tuberculosis. We have presented these guidelines in Table 2 to give a clear overview of what EU/EEA countries could adopt in terms of catchup vaccination[36]. They recommend a full vaccination work up for a recently arrived migrant to Canada, including MMR, DTP for all adults as well as children with uncertain vaccination status, serological testing and vaccination in adults for varicella, and adding hepatitis B vaccination in specific adult and child migrant populations from high-burden countries. The IOM has also recommended vaccination for recently arrived migrants/refugees according the national schedule for the country, with priority for protection against measles, rubella, diphtheria, tetanus, pertussis, polio, Hib and hepatitis B[17]. Whilst

such guidance may be informative for harmonising approaches to vaccination in migrants, our data suggest that there remains a critical need now to generate a comprehensive set of guidelines for the EU/EEA context and – importantly – work towards uptake and implementation of guidance at the national level across the EU/EEA targeting both child and adult migrants in catch-up vaccination. This aligns with priorities of the WHO European Vaccine Action Plan[10], that seek to reduce inequities in access to vaccination in migrant populations in Europe. Strong promotional campaigns and a commitment to improving access to primary care – whilst being mindful of the different experiences that each EU country has with respect to migration demographics and health-care resources – will be crucial for improving the health status of recently arrived migrants across Europe.

TABLE 2. Summary of recommendations from the Canadian guidelines

Vaccine-preventable disease	Children <18 years	Adults >18 years
Measles, mumps, rubella	Vaccinate all migrant children with missing or uncertain vaccination records using age appropriate vaccination	Vaccinate all adults without immunisation record
Diphtheria, pertussis, tetanus, polio	Vaccinate all migrant children with missing or uncertain vaccination records using age appropriate vaccination	Vaccinate all adult migrants without immunisation records
Varicella	Vaccinate all migrant children < 13 years with varicella vaccine without prior serological testing	Screen all migrants from tropical countries of 13 years and older for serum varicella antibodies, and vaccinate those found to be susceptible
Hepatitis B	Screen children where seroprevalence of is >2%. Vaccinate those who are susceptible	Screen adults where seroprevalance of is >2%. Vaccinate those who are susceptible
Tuberculosis	Screen children, adolescent <20 years of age from countries with high incidence as soon as possible after their arrival with a tuberculin skin test. If positive, rule out active tuberculosis and then treat latent tuberculosis infection.	Screen those 20-50 year of age from countries with high incidence as soon as possible after their arrival with a tuberculin skin test. If positive, rule out active tuberculosis and then treat latent tuberculosis infection.

Key points

- There is striking variation in policies relating to the vaccination of recently arrived migrants across Europe. Six (18.8%) countries had comprehensive guidance and regulations specific to the vaccination of migrants, of which in 2 countries guidance only focused on child migrants. It is not clear to what extent guidelines are applied in practice.
- There is heterogeneity in approaches to priority vaccination in child, adolescent, and adult migrants. Polio is the most commonly administered vaccine and other vaccinations according to guidelines analysed – for example hepatitis B – may not be considered.
- Differences were found across countries when migrant presented with missing or incomplete vaccination records and a lack of clarity in terms of how to approach catch-up vaccination
- There is a lack of clarity on optimum approaches to vaccination in migrants, and a need for robust research and data collection in this area to explore and assess what works best in terms of the implementation of vaccination strategies in both child and adult migrants.
- More emphasis must be placed on ensuring migrant-specific guidance is disseminated to front-line healthcare professionals to improve vaccine delivery and uptake in diverse migration populations across the region.

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09

Divergent approaches in the vaccination of recently arrived migrants to Europe: a survey of national experts from 32 countries, 2017

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ABSTRACT

Background

Migrants within the European Union and European Economic Area (EU/EEA) may be underimmunised and lack documentation on previous vaccinations. We investigated approaches to vaccination in recently arrived adult and child migrants, and guideline availability and implementation.

Materials and Methods

Between March and May 2017, a national vaccination expert from every EU/EEA country and Switzerland completed an electronic questionnaire. We used descriptive analyses to calculate percentages, and framework analysis to synthesise free-text responses.

Results

We approached 32 countries (response rate 100%). Although 28 experts reported vaccination guidance at national level, specific guidelines for recently arrived migrants were only available in six countries and not consistently implemented. Twenty-three countries administered vaccinations during on-arrival health checks. Most experts recommended multiple vaccination opportunities be made available: at point of entry (n = 13) or at holding level (reception centres, migrant camps, detention centres) (n = 21). In 30 countries, child migrants without evidence of previous vaccination were re-vaccinated according to the national schedule. Diphtheria-pertussis-tetanus and polio vaccinations were given to migrant children in all countries, measles-mumps-rubella (MMR) in 31 countries, hepatitis B vaccination in 25. Low levels of catch-up vaccination were reported in adult migrants, with only 13 countries offering MMR and 10 countries charging fees.

Conclusion

Existing guidance is often not migrant-specific and may not be applied in practice; clarification is needed on which vaccines should be given. Strategies are needed specifically for catch-up vaccination in adult migrants. Vaccinations should be offered in multiple settings, free of charge, with sufficient guidance and training provided to front-line healthcare professionals.

INTRODUCTION

Ensuring high levels of vaccination coverage is a key priority for the European Union (EU)[1–4]; yet very high levels of both external and internal migration in the region in recent years have posed considerable challenges to achieving this. Migrants, including refugees and asylum seekers, may be underimmunised if they have come from countries whose healthcare system has been disrupted due to war or other circumstances, which makes them vulnerable to acquiring infection if exposed[5–7]. Syrian and Afghan migrants, dominant migrant groups to the EU in recent years[8], have relatively low vaccine coverage rates. For example, immunisation coverage in Syria is around 40% for diphtheria, tetanus and pertussis (DTP) and 50% for polio[9,10]. Greece recently reported vaccination status as 'unknown' in 79.3% of Syrian children during an outbreak of hepatitis A in migrant camps[11]. Outbreaks of vaccine-preventable diseases such as measles have been seen among migrants in Europe, which may reflect sub-optimal vaccination coverage in migrant populations[12,13]. Many migrants lack any documentation of their vaccination history. The role of serology in assessing vaccination status is not clear and clinically relevant information about the usefulness of serology for migrants arriving in host countries is not available. Serological testing is, for example, not recommended for polio in migrants arriving to the United States[14], but it is used for other infections in other groups, for example travellers going abroad and presenting for pre-travel advice. Most countries do not routinely check serology before vaccination of arriving migrants because of cost and logistical issues.

On arrival to the receiving country, migrants may face multiple barriers to accessing healthcare, including catch-up vaccinations[15,16]. Migrants are known to face barriers to accessing primary-care physicians, where most vaccination and screening for infection routinely occurs[17], and may be charged for any healthcare they receive, which may mean that seeking preventative healthcare such as vaccination becomes less of a priority[18]. Undocumented migrants in particular may fear approaching health services because of links with immigration authorities.

The European Vaccine Action Plan (EVAP) has set out a series of goals and objectives for immunisation and control of vaccine-preventable diseases (VPD) in the European Region member states for 2015–20[4], emphasising that special attention should be paid to migrants and marginalised communities, ensuring their eligibility and access to appropriate immunisation services and information. However, strategies and approaches to engaging this group are lacking, as are high-quality studies assessing vaccination implementation in migrant populations[19]. The Promote Vaccination

among Migrant Populations in Europe (PROVOMAX) project, which ended in 2013, sought to promote vaccination among migrants and develop recommendations for policymakers[20]. The European Centre for Disease Prevention and Control (ECDC) Vaccine Scheduler database (https://vaccine-schedule.ecdc.europa.eu) highlights immunisation schedules in all EU countries and allows comparison of vaccination policies between countries[21]. This provides a sense of what every country is doing, but the database does not have data on vaccine schedules for migrants.

There remain numerous questions around optimal vaccination strategies in migrants, including which vaccinations should be prioritised in adult and child migrants and how to promote vaccination uptake in this group and implement effective and cost-effective programmes. We therefore approached national vaccination experts from every EU and European Economic Area (EEA) country and Switzerland to complete an electronic questionnaire survey exploring current and preferred approaches to vaccination in recently arrived migrants, guideline availability and implementation, different approaches in adults and children, the extent to which charges or fees were applied. The survey also contained open-ended questions to allow experts to document promotional activities in migrants and perspectives from across the region.

MATERIALS AND METHODS

Questionnaire development

We developed an electronic 12-point questionnaire survey containing structured and open-ended questions around country-specific vaccination policies for recently arrived migrants in the EU/EEA and Switzerland. Switzerland was included because the country has been hosting large numbers of refugees since 2015. This approach of engaging national experts has been successfully used previously in this field[22]. Questionnaire development was informed by a narrative synthesis of existing literature on migrant vaccination in Europe. For the purposes of this research, we defined recently arrived migrants as foreign-born and living in the host country for less than 10 years. At the top of the questionnaire we alerted experts to the fact that recently arrived migrants included a variety of migrants, specifying definitions for refugees (granted asylum in the host country), asylum seekers (awaiting a decision on their asylum application) and undocumented migrants (without the necessary authorisation or documents required under the host country's immigration regulations). We defined children as individuals aged between 0 and 18 years.

The questionnaire (Supplement 1) included specific questions on the availability of national or regional guidelines for vaccinations in recently arrived migrants, and the extent to which they are applied in practice. In addition, questions were asked about what vaccinations are currently given, differences between adults and children, and the experts' opinions on new approaches, where and what should be offered, approaches adopted for migrants with incomplete vaccination history or lack of documentation, and whether migrants are charged a fee for vaccinations received. In the open-ended questions, we asked experts to provide specific examples of innovative strategies and promotional activities around vaccination and immunisation currently aimed at recently arrived migrants in their countries. The questionnaire was designed to take around 15 min to complete.

Approach and data analysis

Before distributing the survey, we piloted it with two members of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for Infections in Travellers and Migrants (ESGITM). These two interviews were excluded from the analysis but were used to improve the questions and instructions. We amended the questionnaire based on their feedback. We created the ESGITM Working Group on Vaccination of Migrants, a group of European experts on infection and vaccination, and all members of the working group were asked to recommend a vaccination expert in their country. These vaccination experts had to be working at a national level (e.g. the Ministry of Health, a public health institution or equivalent) with expertise relating to vaccination policy and practice in migrants in their specific country. For six countries, for which a recommendation was not given by the ESGITM network, experts were identified through a search of authors of national guidelines and vaccinations documents for that specific country. These experts were contacted and asked whether they could complete the survey for their country or recommend another expert. We aimed to approach one national expert from each country. The questionnaire was sent electronically via email between March and May 2017 to experts in the following countries: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland and the United Kingdom. A first reminder was sent after 2 weeks. A second reminder was sent 1 month later. Experts were asked to complete the electronic form and email it back to us.

Data were extracted from the completed survey forms by two researchers, and inputted into Microsoft Excel, to ensure accuracy before analysis. Descriptive analyses were conducted to calculate percentages and proportions. Framework analysis was conducted to synthesise free-text responses in the open-ended questions[23].

RESULTS

Survey response

All 32 experts from the 32 approached EU/EEA countries and Switzerland returned a completed questionnaire. Eight were working in Ministry of Health teams specifically on migration, 21 in public health teams, three had expertise in vaccination issues related to migrants – for example being part of vaccination advisory groups (18 women, 14 men). Detailed information on the expert group and their expertise can be found in Supplement 2.

Vaccination guidelines: policy vs practice

Twenty-eight of 32 experts reported being aware of guidance at a national level on vaccination within their country, yet guidelines specifically focusing on migrants were only reported by six of 32 experts. Twenty-three experts reported that vaccinations were administered during an on-arrival health check to recently arrived migrants, 29 experts reported that recently arrived migrants were offered a health check within a month after arrival, and in 17 countries, this health check was compulsory. Countries followed the national schedule when seeing a migrant for the first time, with 14 of 32 experts stating that national vaccination guidelines were always applied in practice in migrant patients. Sixteen experts reported that the guidelines were only partly applied in practice, whereas two reported that guidelines were never applied in practice. Experts reported that the extent to which national guidelines (or where available, migrant-specific guidelines), were implemented depended on the number of healthcare staff available, the number of refugees, willingness of healthcare staff and awareness among healthcare staff as to the immunisation needs of presenting migrants.

Differences in vaccination approach between children and adults

The vaccines offered to adults and children varied across countries, according to the experts consulted (Figure 1). DTP, polio and measles-mumps-rubella (MMR) vaccinations were given to migrant children in 31 of 32 countries, with hepatitis B

vaccination being the next most commonly administered vaccine (25/32). In half or less than half of all reporting countries were child migrants offered vaccinations against tuberculosis, meningococcal disease, pneumococcal disease or influenza. Recently arrived adult or child migrants were not vaccinated for hepatitis A in any country. Adult migrants seem to be excluded from catch-up vaccination initiatives in most countries, with experts reporting lower numbers of different vaccinations per person. Adult vaccination mainly focused on catch-up vaccinations for DTP, polio and MMR, but half or less than half of all reporting countries reported offering these vaccinations to adults (diphtheria: 16/32; pertussis: 10/32; tetanus: 16/32; polio: 12/32; MMR: 13/32). Other vaccines were less frequently reported. Data were not collected in this survey on the approach taken when multiple doses of a vaccination are required.

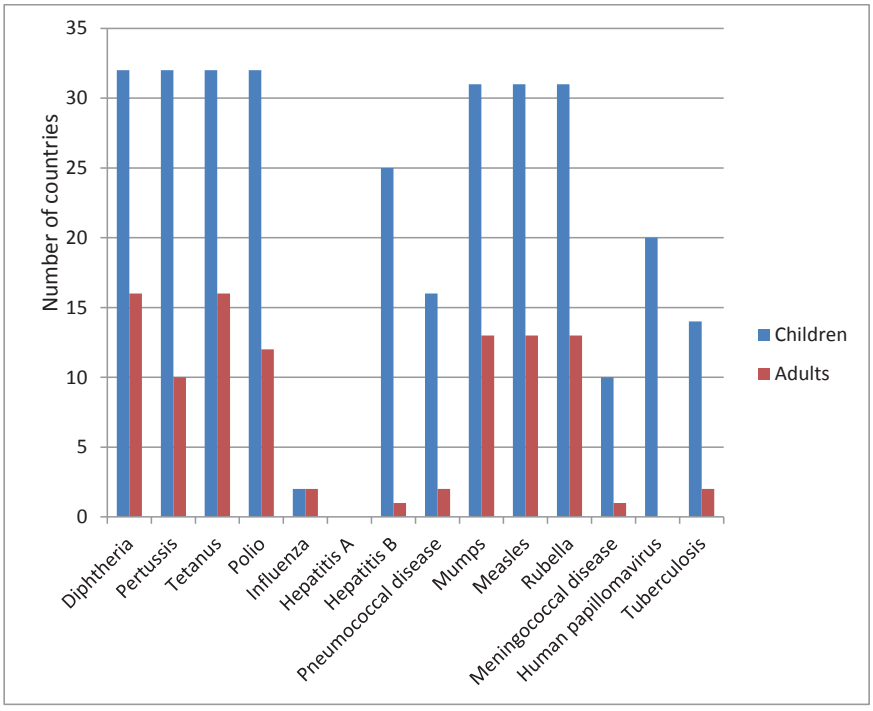

FIGURE 1. Vaccinations administered to adult and child migrants: approaches identified across Europe, 2017 (n = 32 countries)

Approaches adopted for migrants reporting incomplete vaccination history

The approach in migrants with an incomplete vaccination history or a lack of documentation varied by country. In most countries, when there was a lack of evidence of previous vaccination in children, or evidence of incomplete vaccination, they were re-vaccinated according to the national schedule (n = 30). For adults, four countries experts reported that adults in this situation would not be vaccinated for anything. In 18 countries, vaccinations that are prioritised in order to prevent an outbreak were administered to adults, whereas re-vaccination in children occurred according to the national vaccination schedule. One of the 32 experts reported that they would do serological testing before repeat vaccinations in adults.

Financing of vaccination for migrants in the EU/EEA

Ten experts reported that migrants had to pay for their vaccination when approaching statutory services. In three of these 10 countries, experts stated that it was specifically undocumented migrants that had to pay for vaccinations. The need for financial contribution also varied by age; one expert reported that vaccination in children was free of charge and that only adults were charged. Another expert reported that vaccination upon arrival at the first medical check was always offered for free, whereas vaccinations at a later stage had to be paid by certain migrants.

Promotional activities and innovative strategies

Fifteen experts reported initiatives to engage migrants in vaccination and improve uptake, some examples of which are outlined in Table 1. Promotional activities and innovative strategies were organised at different levels of the healthcare system; Table 1 shows the diversity of the strategies across Europe. However, we have no data on how effective or evidence-based these different approaches are, and where leaflets had been translated to make them more accessible they were not always translated into sufficient dominant migrant languages. In addition, it needs to be acknowledged that a lack of literacy in some migrant groups can be a major barrier to healthcare and vaccination.

TABLE 1. Strategies for improving vaccination uptake in adult and child migrants, reported by vaccine experts in the EU/EEA, 2017 (n = 32 countries).

Theme	Examples of activity and strategy
Distribution of promotional material	*Peer-to-peer projects* Sweden: Peer-to-peer project combined with a package of communication material (film, web-based animation, dialogue seminars) in the Somali community based on the Tailoring Immunization Programs mapping with the WHO/Euro tool. *Leaflets developed in different languages* Germany: National level – information leaflets for each relevant vaccine in 20 languages. Bulgaria: Leaflets in the reception centres and refugee camps in Arabic, Farsi and other languages. *Poster and brochure distributed in camps regarding specific infectious disease* Poland: Information sessions were carried out in Centres for Foreigners (both for employees and for asylum seekers) about the importance of getting vaccinated and overall information on vaccine-preventable diseases. Brochures and posters regarding measles are distributed in the camps (prepared in cooperation with the National Institute of Public Health – National Institute of Hygiene).
Education and awareness	*Health education programmes* Distribution of educational material, developed by the International Organisation for Migration, in certain countries. *Information about vaccination distributed to migrants through the (registration) centre on arrival* Switzerland: Information on access to infectious diseases screening, access to care and access to vaccination is mandatory in centres for asylum seekers in federal registration centres and housing centres.
Outreach work	*Nurses visits and advice* Malta: Once migrants arrive, if they are undocumented and are in reception centres, nurses visit, advise and offer vaccines. Other migrants are reached through national immunisation campaigns. *Mobile outreach teams of physicians to migrant communities and reception centres* Reported in Germany. *Vaccination checking in school settings* Cyprus: "For children going to school, the school health services are very active in promoting the immunisations by checking all students for completeness of their vaccinations by asking them to present their immunisation cards. The parents of those students who don't have the necessary vaccines are contacted by phone by the school health visitor and they are asked to complete the missing vaccines for their child."
National advocacy	*National immunisation campaigns* Reported in Malta. *Recommendations for vaccination promotion by health agencies and professionals* Austria: Targeted recommendations for vaccination upon first medical check, distributed to all involved stakeholders. *Governmental walk-in centres offer free vaccination for migrants* Cyprus: "People can get vaccinated or vaccinate their children in government walk-in centres completely free of charge. There are 63 such immunisation centres spread across Cyprus in cities and also in small communities."

Recommendations to improve vaccination strategies in migrants

Most experts agreed that EU-level guidelines on the vaccination of migrants are needed (n = 26). Nineteen experts believed that vaccination should be better promoted. Other experts emphasised the need for detection of vaccine-preventable diseases (n = 6) and called for a new surveillance system to record information on vaccination status in asylum seekers. In addition, costs of vaccinations should be covered by national organisations (n = 4).

To improve uptake of vaccination, experts highlighted that multiple opportunities for catch-up vaccination should be offered to adult and child migrants after arrival to the EU/EEA. Vaccination should be offered primarily at the point of entry or at a holding level (i.e. in reception centres, migrant camps and detention centres) (Figure 2).

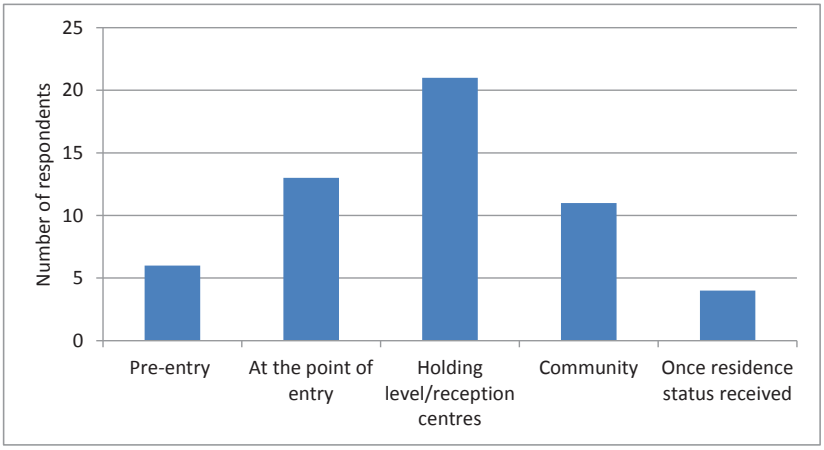

FIGURE 2. Vaccine experts' opinion on when vaccinations should be offered to adult and child migrants, EU/EEA, 2017 (n = 32 countries)

DISCUSSION

Vaccination policies across Europe in relation to both adult and child migrants vary widely. Experts reported that national vaccination guidelines are used and these guidelines contain information on how to approach migrant patients with missed vaccinations and to offer catch-up vaccinations. However, these guidelines are often not migrant-specific and are frequently not applied in practice, particularly in relation to catch-up vaccination in adult migrants. Considerable variations in

approaches exist between adults and children; children mostly enter the national vaccination schedule, whereas adults receive no catch-up vaccination or priority vaccinations only. The experts from 10 of 32 countries reported that migrants have to pay for vaccination. Almost half of the experts reported initiatives to promote vaccination among migrant groups, but evidence for a sound theoretical basis is lacking. Experts stated that better promotion for vaccination is needed and implementation should be strengthened.

Priority is given to child vaccination in most EU/EEA countries. Vaccination guidelines include recommendations for children with incompletely vaccination. However, recommendations on the catch-up schedule to follow in case of missed vaccinations for both adults and children may vary by vaccine and by country. A study in 2011 that assessed immunisation policies across all EU/EEA countries – although not migrant-specific – found that all 27 countries recommended MMR and polio vaccinations for children, and only 11 of the 27 countries included MMR and polio vaccine for adults[24]. This concurs with our results pertaining to migrants, where vaccination for MMR and polio in migrant children is reported in all included countries and vaccination of adults only in half of the EU/EEA countries; this is despite the fact that some migrants originate from countries where health systems may have broken down resulting in immunisations being missed[25,26]. The Canadian guidelines, based on a systematic review of available evidence, recommend that MMR, DTP, polio, varicella and hepatitis B vaccines should be given to children and adult migrants[27], whereas our survey highlights that in more than half of EU/EEA countries these would not routinely be offered to adults and thus this represents an area requiring policy development[10]. Measles vaccine should be considered in both children and adult migrants in light of the fact that there have been outbreaks of measles in the EU that have been linked to migrant populations specifically, and there is a drive to eliminate measles in the European region[12,13]. Experts reported that hepatitis A was not routinely given, despite outbreaks of hepatitis being reported in migrant camps in Europe[11], yet the benefits of vaccinating migrants for hepatitis A may well be context-specific and something that needs to be considered a priority in camp and transit settings and/or focused on at-risk groups. EU/EEA countries may need to be mindful of additional vaccines such as influenza, hepatitis B and varicella vaccines that may need to be offered to migrants depending on living conditions, season and the epidemiological situation.

Barriers that have been shown to hinder adult vaccination uptake in general include lack of coordination, inability to pay and a lack of recommendation by healthcare providers[28,29], which echoes our findings pertaining to recently arrived migrants.

Most migrants and refugees will not routinely be given a portable health record on arrival to the EU/EEA, so if they do get vaccinated in a transit or arrival country, this may result in duplication and/or confusion as to which vaccinations to give on arrival in the final destination country. The role of portable health records to ensure that a record is made of the vaccinations given at various points in the migration trajectory, with the aim of preventing duplication of vaccination, was not something we explored in this survey, but is an area that needs to be better considered. The International Organization for Migration (IOM), co-funded by the EU Third Health Programme, is currently piloting general health and vaccination assessments and exploring the role of electronic personal health records (e-PHR) in certain migrants arriving to Croatia, Greece, Italy and Slovenia as a tool for integration of refugees into EU health systems (https://greece.iom.int/en/re-health). To implement guidelines more effectively, the experts we approached recommended strong promotional campaigns and a harmonised vaccination schedule, which has been reported by others[5,30]. Educational activities to promote vaccination uptake by migrants were diverse, but the impact of these activities has not been well researched to date. These educational activities may benefit from further European collaboration, which has the potential to facilitate exchange of material in the appropriate languages and exchange of methods with measurable effects on vaccination uptake. The experts we approached called for EU-level guidelines to inform optimal approaches, which would support the goals of the European Vaccine Action Plan. Differences in countries' healthcare systems and vaccine delivery structures need to be addressed[31]. Early access to primary care providers may be helpful in coordinating vaccine campaigns; yet it is unclear to what extent different countries have charging systems in primary care specifically for vaccination and this is not something we asked about in our survey. Another major challenge in terms of implementation is that countries across Europe face vastly different migrant situations – for example, transit countries such as Greece and Italy have large numbers of refugees arriving who may be temporary, which has implications for guideline development. The financing of vaccination programmes also needs to be considered in the context of migration. To improve uptake of vaccination in migrants, costs for key vaccinations should ideally be free of charge for migrants who are unable to pay, with European governments being mindful of their commitments to ensure equitable access to vaccines to meet target 3.8 of the Sustainable Development Goal on health to provide "access to safe, effective, quality, and affordable essential medicines and vaccines for all"[32]. Routine checks of vaccination status in medical files may facilitate the identification of missing vaccinations that can be addressed if migrants visit statutory healthcare providers after arrival.

Clinicians and policymakers should also be mindful that both EU migrants – moving from one country in Europe to another – and non-EU migrants that were the focus of our survey, may be underimmunised and at increased risk for vaccine-preventable diseases; highly mobile EU migrants moving from eastern Europe to western Europe are a focus of the recent large multi-country measles epidemic in Europe[32]. In addition, more research is needed to explore catch-up vaccination in adolescent migrants who – alongside the adults identified in our survey – may also be an underimmunised group who are excluded from initiatives to assess immunisation status and offer appropriate catch-up vaccination, with national vaccination initiatives largely focused around children under 5 years of age[7,32]. In a cohort of asylum seekers in Denmark, 401 (48%) of 842 adolescents (aged 10–17 years) were reported as unimmunised or status unknown[7]. Further, it is important to note that migrants are one of several potentially underimmunised groups in the EU/EEA region. Data are lacking to what extent underimmunised groups contribute to outbreaks of vaccine-preventable diseases in the region, and improving data collection around migrant status and vaccine-preventable diseases, is an important next step. Table 2 summarises key points of action.

A limitation of our study is that we asked one expert at national level for each specific EU/EEA country and Switzerland, which may mean we have missed documenting regional differences. In addition, although we clearly defined at the top of the questionnaire the types of recently arrived migrants that we were aiming to capture data on, an expert's own definition of a migrant may have meant that some answers did not fully represent the target group. Our experts were all working in the Ministry of Health or in public health, but we are aware that there are other entities providing vaccination, e.g. non-governmental organisations. We cannot conclude from our findings that the policies we have documented are applied in practice country-wide. A strength of our study is that we included all 32 EU/EEA countries and Switzerland, with a previous study exploring similar issues in six countries[33].

Conclusion

Our data show that there is a need for migrant-specific guidelines on vaccination approaches for both children and adults in the EU/EEA. To improve uptake, guidelines on vaccination in migrant populations should include specific information on implementation. Further European collaboration has the potential to strengthen initiatives to improve vaccination uptake in underimmunised migrant groups.

TABLE 2. Findings and points of action for governments, researchers and policy makers proposed by the vaccine expert survey, 2017 (n = 32 EU/EEA countries).

Findings	Suggested solutions
• There are a variety of approaches to vaccination of both adult and child migrants across the EU/EEA.	• Develop EU-level guidelines for vaccination of recently arrived adult and child migrants, with clarification given on which vaccines should be offered.
• Where guidance exists, it is in most cases not migrant-specific and often not applied in practice.	• Multiple approaches are needed to engage and promote vaccination uptake in migrants, across multiple locations.
• Considerable variation in approaches exists between adults and children. Child migrants with uncertain vaccination status are in most countries re-vaccinated according to the national vaccination schedule. Adults often receive no catch-up vaccination, or for priority vaccinations only.	• Vaccination needs to be free of charge for all migrant groups, including undocumented migrants.
• Adult migrants may be charged for vaccinations received at statutory health services in some countries, which may deter them from seeking vaccination and other preventative healthcare.	• Better explore models of best practice from across the EU/EEA to assess innovative strategies to improve vaccine delivery to adult and child migrants.
• There is considerable variation among experts as to which vaccines should be offered to recently arrived migrants, particularly adults, and experts call for clear evidence-based guidance on this issue.	• High quality studies are needed assessing vaccination implementation and cost-effectiveness in migrant populations.
• It is unclear where vaccination should be offered to improve uptake. Most experts agreed that focus should be soon after arrival, at the holding level (reception centres, refugee camps or detention centres) and be better promoted.	• Explore options for improving data collection and surveillance on vaccination coverage and burden of vaccine-preventable diseases in migrant populations across Europe.
	• Explore options for improving data capture to avoid duplication of efforts and unnecessary repeat vaccination along the migration trajectory (for example by non-governmental organisations in transit camps and also at statutory health services) after arrival to Europe (e.g. use of mobile phones, electronic vaccination cards and personal health records).
	• Explore the role of migrants (including underimmunised internal EU migrants and of adolescent and adult migrants), in outbreaks of vaccine-preventable diseases in the EU through robust research, and identify strategies to facilitate improved vaccine coverage in these groups.

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Supplement 1

ESGITM/ESCMID survey of policy and guidance for vaccinations in migrant populations across Europe

ESGITM/ESCMID survey of policy and guidance for vaccinations in migrant populations across Europe

We would value your input into a 12-point survey to explore how EU countries approach vaccination in recently arrived migrants, on behalf of the European Study Group for Infections in Travellers and Migrants (ESGITM/ESCMID).

For the purposes of this survey, definitions are:

- ***Recently arrived migrant*: Foreign-born, in the host country for <10 years**
- ***Refugee*: Granted asylum in the host country**
- ***Asylum seeker*: Awaiting a decision on their asylum application in host country**
- ***Undocumented migrant ("irregular migrant")*: Without necessary authorisation or documents required under host country's immigration regulations.**

After completing the questionnaire, please return this form to: s.j.ravensbergen@umcg.nl

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Name: Click here to enter text.

Position: Click here to enter text.

Area of expertise: Click here to enter text.

Country of origin: Click here to enter text.

1. Are you aware of policies or guidelines for vaccinating recently arrived migrants in your country?
   - ☐ Yes, at a national level
   - ☐ Yes, but only in some regions of the country
   - ☐ There are no migrant-specific policies
   - ☐ Other: Click here to enter text.

2. For which migrant groups are there specific vaccine policies/guidelines in your country? [Select ***all*** that apply]
   - ☐ Recently arrived migrants
   - ☐ Refugees or asylum seekers only
   - ☐ Undocumented migrants
   - ☐ Any other groups: Click here to enter text.

3. Are recently arrived migrants offered a health check on arrival (within a month)?
   - ☐ Yes
   - ☐ No
   - ☐ Later than a month

   If yes:
   Is this health check compulsory?
   - ☐ Yes
   - ☐ No

   Does the health check include questions on previous immunizations?
   - ☐ Yes
   - ☐ No

   Are any vaccinations actually offered/administered at this health check?
   - ☐ Yes
   - ☐ No

4. For child and adult migrants, please indicate which vaccines:
   - Are **routinely** given in your country;
   - Are **mandatory** in your country;
   - **You would recommend**

   [Please place an "X" in the box for all that apply]

Disease	**Children**			**Adults**		
	Routine	Mandatory	Recommend	Routine	Mandatory	Recommend
Diphtheria	☐	☐	☐	☐	☐	☐
Pertussis	☐	☐	☐	☐	☐	☐
Tetanus	☐	☐	☐	☐	☐	☐
Polio	☐	☐	☐	☐	☐	☐
Influenza	☐	☐	☐	☐	☐	☐
Hepatitis A	☐	☐	☐	☐	☐	☐
Hepatitis B	☐	☐	☐	☐	☐	☐
Pneumococcal disease	☐	☐	☐	☐	☐	☐
Mumps	☐	☐	☐	☐	☐	☐
Measles	☐	☐	☐	☐	☐	☐
Rubella	☐	☐	☐	☐	☐	☐
Meningococcal disease	☐	☐	☐	☐	☐	☐
Human papillomavirus	☐	☐	☐	☐	☐	☐
Tuberculosis	☐	☐	☐	☐	☐	☐
Other [please state]	Click here to enter	Click here to enter text.	Click here to enter text.	Click here to enter	Click here to enter text.	Click here to enter text.

	text.			text.		

5. What is done for recently arrived **CHILD** migrants with incomplete vaccinations or no vaccination history? [Select ***all*** that apply]
   - ☐ Don't vaccinate for anything
   - ☐ Give all vaccinations according to national schedule
   - ☐ Only give priority vaccinations
   - ☐ Test for immunity prior to vaccinating, then vaccinate accordingly

6. What is done for recently arrived **ADULT** migrants with incomplete vaccinations or no vaccination history? [Select ***all*** that apply]
   - ☐ Don't vaccinate for anything
   - ☐ Give all vaccinations again according to national schedule
   - ☐ Only give priority vaccinations
   - ☐ Test for immunity prior to vaccinating, then vaccinate accordingly

7. Do any migrants have to pay themselves "out of pocket" for some or all of their vaccinations?
   - ☐ Yes
   - ☐ No

   If yes, which migrant groups have to pay for vaccinations?
   - ☐ All recently arrived migrants
   - ☐ Refugees or asylum seekers only
   - ☐ Undocumented migrants only
   - ☐ Other: Click here to enter text.

8. In your opinion, at what stage in the migration process should vaccinations be given?
   - ☐ Pre-entry in countries of origin
   - ☐ At the point of entry
   - ☐ Holding level (reception centres, refugee camps, detention centres)
   - ☐ Post arrival at the community level
   - ☐ Once residence status received (e.g. granted asylum)
   - ☐ Other: Click here to enter text.

9. Are there any activities to promote vaccination among **recently arrived migrants** in your country, e.g. educational awareness campaigns, leaflets on arrival, outreach programmes?
   - ☐ Yes
   - ☐ No

   Please describe any examples of best practice or innovative initiatives that take place in your country: Click here to enter text.

10. Where policies / guidelines for migrant vaccination exist, in your opinion are they applied in practice?
    - ☐ Yes, always
    - ☐ In some circumstances: Click here to enter text.
    - ☐ Never/rarely

11. In your opinion, what needs to change in terms of current approaches/policies/guidelines in your country? [Select ***all*** that apply]
    - ☐ Develop migrant-specific policies/guidelines
    - ☐ Nothing, current policies/guidelines are adequate
    - ☐ Lower costs for vaccines for migrants
    - ☐ Improve detection of vaccine preventable infectious diseases
    - ☐ Better promote and improve access to vaccines for recently arrived migrants
    - ☐ Others: Click here to enter text.

12. Do you think there should be EU-level guidelines for vaccinations in recently arrived migrants?
    - ☐ Yes
    - ☐ No

On behalf of ESGITM/ESCMID, we would like to thank you for filling in this questionnaire.

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University Medical Centre Groningen, The Netherlands
Prof Dr Ymkje Stienstra
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Supplement 2

Table detailing the institutions of the participating European experts

Country	Institution	Area of Expertise
Austria	Federal Ministry of Health Austria	Vaccination
Belgium	Fedasil – federal agency for the reception of asylum seekers	General medicine, tropical medicine, migrants' health
Bulgaria	Ministry of Health	Epidemiology of infectious diseases
Croatia	National Infection Control Advisory Board of the Croatian Ministry of Health	Infectious Diseases, Health Care Associated Infections, Prevention, Vaccination
Cyprus	National Focal point for vaccine preventable diseases	Infectious Diseases, Public Health
Czech Republic	Deputy Minister of Health	Vaccinologist, public health specialist
Denmark	Statens Serum Institut	Infectious diseases, Public Health
Estonia	Public Health Department of the Ministry of Social Affairs	Communicable diseases
Finland	Vaccination Programme Unit, National Institute for Health and Welfare (THL)	Immunization programs, infectious diseases, international health
France	Office "Population Health and Immunization Policy", Ministry of Health and Social Affairs	Population Health and Immunization Policy
Germany	Immunization Unit, Robert Koch-Institute	Immunization policy-making
Greece	Hellenic Center for Disease Control and Prevention Athens, Head of Travel Medicine Office	Public Health, Travel Medicine
Hungary	Hungarian Association of Public Health Training and Research Institutions, WHO Public Health Aspects of Migration in Europe	Migration health
Iceland	Directorate Of Health, Centre for Disease Control	Infectious Diseases and Public Health
Ireland	Health Protection Surveillance Centre | Health Protection Surveillance Centre, Public Health Medicine	Surveillance, epidemiology
Italy	Office 5-Prevention of communicable diseases and International Prophylaxis	Infectious diseases
Latvia	Ministry of Health of the Republic of Latvia, Public Health Department	Senior Expert in the Field of Epidemiological Safety Issues
Liechtenstein	Chief Medical Officer	Public Health

Country	Institution	Area of Expertise
Lithuania	Faculty of Medicine, Public Health Institute	Vaccination
Luxembourg	Ministry of Health	Public Health
Malta	Superintendent of Public Health, Ministry of Health	Public Health
The Netherlands	National institute for public health and the environment, Ministry of Health	Vaccine preventable diseases
Norway	Norwegian Institute of Public Health, Chief Medical Officer	Vaccines and vaccination
Poland	Ministry of the Interior and Administration	Medical Sciences, Epidemiology, Infectious and non-infectious diseases
Portugal	Public Health Authority	International Public Health
Romania	Vaccine Advocacy Group	Family Medicine
Slovakia	Ministry of Health	Epidemiology of infectious diseases, vaccinology
Slovenia	Molecular Microbiology and Slovenian HIV/AIDS Reference Centre	Specialist in Clinical Microbiology
Spain	National Referral Unit for Tropical Diseases. Infectious Diseases Department	Infectious Diseases, Public Health
Sweden	Public Health Agency of Sweden, Karolinska Institutet, Head of Unit	Vaccinology
Switzerland	Infection Control and Immunization Program section, communicable Diseases Division, Federal Office of Public Health	Public Health, communicable diseases, immunizations, pediatric infectious diseases
United Kingdom	European Centre on the Health of Societies in Transition, Public Health	Immunisation

10

Asylum seekers' perspectives on vaccination and screening policies after their arrival in Greece and The Netherlands

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ABSTRACT

Introduction

Europe has been dealing with an increasing number of refugees during the past 5 years. The timing of screening and vaccination of refugees is debated by many professionals, however refugees' perspectives on health issues are infrequently taken into account. In this study, we aimed to investigate asylum seekers' perspectives on infectious diseases screening and vaccination policies.

Materials and Methods

Interviews were conducted in Greece and the Netherlands. Asylum seekers and recently arrived refugees were approached and informed with the help of interpreters; consent forms were acquired. The survey focused on demographic data, vaccination status, screening policies and prevention of infectious diseases.

Results

A total of 61 (43 male, 70.5%) refugees (30 Afghanis, 16 Syrian, 7 Eritrean) were interviewed. Mean age was 35.2 years (SD 13.5) and 50% had received primary or secondary education, while 24.6% received none. Median time after arrival in Greece and the Netherlands was 24 months (IQR 8.5-28). 44 out of 61 (72.1) participants were willing to be vaccinated after arrival in Europe, 26 preferred vaccination and screening to be performed at the point of entry. The need for screening and vaccination was perceived higher amongst participants in Greece (100% vs 43.3%) due to living conditions leading to increased risk of outbreaks.

Conclusion

Participants were willing to communicate their perspectives and concerns. Screening and vaccination programs could be more effective when implemented shortly after arrival and by involving asylum seekers and refugees when developing screening and vaccination interventions.

INTRODUCTION

Political turmoil, warfare and instability, specifically in Middle Eastern and African countries, during the past few years have led to an increase in refugees and asylum seekers entering Europe. In the Netherlands, 15.410 asylum seekers have arrived between January 2018 and October 2018[1]. In Greece, 29.404 refugees have arrived overseas between January 2018 and November 2018, while the estimated arrivals through mainland are over 12.000 for the same period. Asylum seekers mostly originate from Syria, Iraq and Afghanistan[2].

Crowded conditions in refugee camps or settlements and the lack of systematic medical care during their transnational journey, may contribute to the dispersion of infectious diseases among this vulnerable group. Therefore, vaccinations and infectious diseases screening programmes in the hosting countries aim to protect public health by preventing dissemination of infectious diseases[3,4].

A recently published study showed a variety of approaches towards vaccination of both adult and child migrants across the EU/EEA. In addition, most guidance is not always migrant specific and the available guidance is frequently not applied in practice[5]. A recent systematic review documenting the effectiveness of European approaches towards migrant screening revealed that in European countries migrants are screened mostly in vertical disease programs, commonly active or latent tuberculosis, or both.

Although recommendations have been made regarding refugees' vaccination policies, a WHO report in 2017 revealed that less than a third of countries have migrant specific guidelines on immunisation in their national programmes and documented differences in policy, guidance, and implementation[6]. Moreover, several studies have shown a high prevalence of micro-organisms expressing antimicriobial resistance (AMR) in the asylum seeker population. Specifically regarding asylum seekers in the Netherlands, it has been shown that prevalence of such microbes is higher compared to the general Dutch population[7], supporting AMR screening at hospital admission.

Furthermore, the optimal timing for implementation of screening and vaccination activities is frequently debated[8,9]. The stressful and dependent situation for asylum seekers upon arrival is considered to complicate free decision making by asylum seekers on health issues. Limited data is available regarding asylum seekers' perspectives on such policies.

In this study, we aimed to investigate the perspectives of refugees and asylum seekers regarding screening and vaccination policies in order to obtain helpful information on the optimal strategy and especially its timing within the migration process. This knowledge could be used in decision making regarding optimal screening and vaccination programmes and their implementation.

MATERIALS AND METHODS

Study setting

Interviews were conducted in Greece and in the Netherlands in order to include asylum seekers at different stages of their asylum seeking journey and document possible differences regarding their perspectives on vaccination and screening policies.

Greece

Interviews were conducted, between May and June of 2018, at the Structure of Welcoming and Hosting of Refugees, Schisto, Athens. Refugee camps in Greece are under the authority of the Greek Ministry of Migration. In order to conduct the study, all necessary forms were sent to the Ministry and we were granted special permission to access the camp in Schisto. The refugee camp has been operational since February 2016 and has a capacity of approximately 1000 refugees. The Structure functions under the administrative and financial supervision of the Ministry of Migration. At the time of the study, 880 refugees were hosted at the camp. Asylum seekers residing at the structure were approached by our team with the help of an interpreter at the communal places of the structure.

The Netherlands

The interviews were conducted in various locations including the offices of ‘Vluchtelingenwerk’, a non-governmental organization, between October of 2017 and February of 2018. Other locations were the tuberculosis center and the department of Internal Medicine of the UMCG. These departments often provide medical care for asylum seekers. Patients were approached during admission or during outpatient visits.

Approach and data analysis

Asylum seekers and refugees were approached with the help of an interpreter and the study was thoroughly explained to the participants. All professional interpreters

were officially trained and certified to communicate and work with asylum seekers. Interviews were conducted in English, Dutch, or any other language with assistance by a professional interpreter in person or by phone.

Data was anonymously recorded using the Qualtrics survey program. The interviews were carried out until data saturation was noted independently by two researchers. Data was analyzed using the statistical software SPSS (SPSS Inc., version 23.0, Chicago, Illinois) and Excel (Microsoft Excel 2016). Descriptive statistics were used to calculate percentages. Open coding was used to analyze the qualitative information from the open-ended questions on the questionnaire.

Throughout the paper Greece and the Netherlands will be referred to as the hosting countries.

Questionnaire development

A semi structured questionnaire was designed to investigate the perspectives of asylum seekers with regard to vaccination and screening in the hosting countries. The questionnaire was composed for the purpose of the study under the guidance of an experienced health psychology researcher (A.V.R.) in University Medical Center Groningen (UMCG), because no standard questionnaire was available for this topic.

The questionnaire was divided into three main parts; the first part was vaccination oriented, the second part focused on screening of multidrug-resistant organisms (MDRO) and tuberculosis and the third part involved questions regarding infectious diseases screening in general followed by a brief discussion on this topic. Considering different educational backgrounds of the participants and the complexity of terms like vaccination and screening, various verbal approaches by the interpreters were used, in order to simplify the questions. In addition, we used visual aids, such as photos of medical equipment used in screening and vaccination, i.e. syringes, swabs and x-rays.

The estimated duration of the interview was approximately 50 minutes. Prior to the start of the study, five pilot interviews were conducted. Potential ambiguities were identified and the questionnaire was revised accordingly. An online tool was used (Qualtrics) during the interviews, to enter the data and record the answers. Participants were reminded of the option not to answer specific questions of the survey in case they did not want to or could not.

Inclusion criteria

Asylum seekers or refugees that arrived in the hosting countries, at least 4 months prior to the study, were included in the study to allow interviewees to form an opinion based on the experiences in the first months after arrival. In addition, only asylum seekers or refugees who arrived in the hosting countries after 1/4/2014 were included, so that interviewees would be able to recollect their experiences with vaccination and screening procedures. Asylum seekers younger than 18 years old were excluded. Information on children vaccination was obtained by interviewing their caretakers.

Ethics

In Greece the study was approved by the Hellenic Centre for Disease Prevention and Control and the Ministry of Migration (protocol number ΚΠ 15161/2017-02/11/2017, 3/3908/03.04.2018). In the Netherlands, this study was evaluated by the Ethics committee and was waived in accordance with Dutch Legislation University Medical Centre Groningen, METc number non-WMO METc 2017/294. A written informed consent was obtained by all included participants. All participants were given the option to withdraw from the study at any given moment without having to give an explanation and were reassured that any potential withdrawal would have no impact in their health care and asylum status.

RESULTS

General characteristics

Table 1 and Table 2 show the general characteristics of the total of the study group and by country were the interviews were conducted, respectively. In total, eight asylum seekers refused to participate, with the main reasons being timing (n=3), exhaustion because of fasting during Ramadan (n=2), cultural limitations to talk to a male interpreter without their spouse present (n=2), and lack of opinion on the discussed subjects (n=1).

In total, 61 (former) asylum seekers and recently arrived refugees were included in the study. 31 of the interviews were conducted in Greece. The majority of participants originated from Afghanistan and Syria, while nine participants originated from Sub-Saharan countries. The most commonly used languages during the interview were Farsi (47.5%), Arabic (16.4%) and English (14.1%). All interviews in Greece were conducted in person with the assistance of professional interpreters. In the

Netherlands all interviews were conducted in person, 14 of which without the help of a professional interpreter, in English(n=8) or in Dutch (n=6), while the remaining 16 interviews were conducted with the help of a professional interpreter over the phone.'

TABLE 1. General characteristics of the total of the 61 participants interviewed in both Greece and the Netherlands.

	Number of interviewees (n=61)
Sex (male %)	43 (70.5)
Age (SD)	35.2 (13.5)
Number of months in hosting country median (IQR))	24.0 (8.5-28.0)
Country of origin (%)	
Afghanistan	30 (49.2)
Syria	16 (26.2)
Eritrea	7 (11.5)
Others*	8 (13.1)
Educational level (%)	
No education	15 (24.6)
Primary education	8 (13.1)
Secondary education	17 (27.9)
Bachelor's/master's	21 (34.4)
Profession (%)	
Construction worker	11 (18.0)
Health care worker	10 (16.4)
Teacher	6 (9.8)
Carpenter	5 (8.2)
Seamstress	4 (6.6)
Others	25 (41.0)
Asylum granted (%)	37 (60.7)

TABLE 2. General characteristics of the participants that were interviewed by country in which the interviews were conducted.

	Greece (n=31)	**Netherlands (n=30)**
Sex (male %)	23 (74.2)	20 (66.6)
Age in years (SD)	34.1 (13.3)	37.2 (14.1)
Number of months in hosting country, median (IQR))	24 (9-27)	25 (8.5-37.25)
Country of origin (%)		
Afghanistan	29 (93.5)	1 (3.3)
Syria	0	16 (53.3)
Eritrea	0	7 (23.3)
Iraq	1 (3.2)	1 (3.3)
Iran	1 (3.2)	0
Others	0	5 (16.7)
Educational level (%)		
No education	15 (48.4)	0
Primary education	4 (12.9)	4 (13.3)
Secondary education	7 (22.6)	10 (33.3)
Bachelor's/master's	5 (16.1)	16 (53.3)
Profession (%)		
Construction worker	8 (25.8)	3 (10.0)
Carpenter	5 (16.1)	0
Seamstress	3 (9.7)	1 (3.3)
Health care worker	1 (3.2)	9 (30.0)
Teacher	2 (6.4)	4 (13.3)
Others	9 (29.0)	13 (43.3)
Asylum granted (%)	11 (35.5)	26 (86.6)

PART A: VACCINATION DATA AND PERSPECTIVES

Vaccinations in adults

53 out of the 61 participants (86.9%) had been vaccinated in their country of origin according to the national vaccination schedule. Only 22 out of the 61 (36.1%) participants were asked about their vaccination status by official authorities, health care workers or NGOs upon arrival in the hosting countries. 12 out of 61 subsequently

received additional vaccinations (influenza (n=2), polio (n=1), tetanus (n=1), hepatitis B (n=1), unknown (n=7)). Vaccination was mostly performed by Non-Governmental Organizations (NGO, n=3) and National Healthcare Employees (n=4).

Vaccinations in children

34 out of 61 (55.7%) participants had children under their care upon arrival in the hosting countries, of which 24 were asked regarding the children's vaccination status. 31 out of 34 (91.2%) participants mentioned that the children had been vaccinated in their country of origin. 27 reported that the children received additional vaccinations in the hosting countries. The most frequently mentioned vaccinations were MMR (n=3), DTP (n=3), measles (n=2) and mumps (n=1). 13 could not recall which vaccines were given to the children. Children were mainly vaccinated by NGOs (n=10), public health care facilities (n=6), or a doctor at the asylum centre (n=5).

Perspectives on vaccination

When asked regarding necessity of vaccination, all 31 participants interviewed in Greece perceived the need of vaccination as of high importance, while only 13 out of the 30 participants interviewed in the Netherlands expressed the same opinion. Point of entry in Europe was considered as the optimal timing for vaccination (n=26), followed by holding level (n=9). Reasons given regarding the optimal timing for vaccination was 'to protect ourselves' (n=21) and 'to stop diseases' (n=8). According to the opinion of the participants, it is of no importance by which organization the vaccination is performed, as long as it is performed (n=25). Other preferences for the organizations performing vaccination were the public health care system (n=11) and NGOs (n=8).

Willingness and necessity of vaccination

In Greece, all 31 participants were willing to be vaccinated. In the Netherlands, 13 out of 30 were willing to be vaccinated. In order to have a better understanding on the perceived importance of vaccination by the participants, we included a question with specific amounts of money and whether the participants were willing to pay them in order to be vaccinated. When asked if participants were willing to pay €10,- for vaccination, 26 out of 31 responded positively in Greece, and 13 out of 30 responded positively in the Netherlands. When asked if participants were willing to pay €200, 12 out of 31 in Greece and only 1 out of 30 in the Netherlands responded positively.

55 participants considered increasing the vaccination rate among asylum seekers to be necessary. Explanations given for the wish to increase general vaccination was ‘for protection’(n=13), ’for prevention’ (n=11), ‘for vulnerable population’ (n=8) and ‘for overall health improvement’(n=6).

Perspectives on promotional work

55 out of 61 participants considered promotional work on vaccination useful to increase the vaccination rate among asylum seekers. 29 participants emphasized the importance of increased educational activities such as seminars/presentations within the hosting facilities, while 8 preferred distribution of written informative material and 4 preferred outreach programmes.

PART B: SCREENING OF INFECTIOUS DISEASES

Hospital admissions and screening for MDRO

13 participants had experienced a hospital admission in the hosting countries, mostly at the department of pulmonary diseases (n=5) and surgery (n=4). During hospital admission, eight asylum seekers communicated with the medical staff with the help of professional interpreters.

Screening for MDRO was performed in three participants. One of them was informed regarding the rationale behind the screening. Nobody had any comments on how the MDRO screening could be improved.

Screening for tuberculosis and scabies

24 participants reported to have been screened for tuberculosis by X-Ray on arrival in the hosting countries. Eight participants were aware of the procedure prior to entering the hosting country, of which four were informed by friends or family members. The remaining four participants were informed by other resources, such as leaflets distributed in the camps and media. Two participants considered the TB screening as a negative experience. One of them was experiencing physical pain due to other health problems during the screening, while the other one reported the experience as negative due to lack of privacy especially when performed by a medical professional of the opposite sex.

Regarding scabies, 19 reported to have been screened for scabies on arrival in the hosting countries, mainly in Greece (n=17). The general experience was described as satisfactory (n=18), with the exception of one participant who indicated that not

all of his clothes were returned after they were washed. 17 interviewees considered the screening to be necessary in order to decrease the burden of scabies. No further comments were made by the interviewees in order to improve the screening for tuberculosis and scabies.

PART C: OTHER PERSPECTIVES ON INFECTIOUS DISEASE SCREENING

53 participants considered screening for infectious diseases useful during the asylum procedure. Main reasons included prevention of infectious diseases among the asylum seeker population (n=14), protection of their own health (n=11), important for the health of both asylum seekers and non-asylum seekers population (n=11), overall health improvement (n=8) and the vulnerable aspect of the asylum seekers population (n=7). Seven participants opted not to answer this question.

Participants preferred to expand infectious diseases screening policy for asylum seekers in order to include hepatitis B (n=34), hepatitis C (n=31) and HIV (n=30). The majority of the participants were particularly concerned regarding sexually transmitted diseases (STDs) and would like themselves and other asylum seekers to be screened for STDs. Point of entry in Europe was considered as the optimal timing (n=42) for such screening, followed by holding level (n=6) and country granting asylum (n=2). Participants expressed concern regarding asylum seekers' sexual health even after arrival in the hosting countries. A recurring theme during the interviews was the conception that different culture and social behavior in the hosting countries could lead to more liberal sexual behavior and extra marital sex, without the knowledge how to protect one's health.

When asked to elaborate and further comment on infectious diseases screening and vaccination implementation, the participants mainly focused on the importance of efficient systematic medical care (‘*good health is above all*’, ‘*first comes health*’) and infectious diseases control (‘*need to protect ourselves and others*’), while one of the participants used a rather relevant Afgani proverb, *‘when one sheep is sick then all sheep are sick’*. The main complaint expressed was insufficient medical care and/or understaffed structures (n=9). Seven suggested that more information on health care and infectious diseases should be available. Particularly in Greece, four of the participants expressed concerns regarding scabies outbreaks and skin disorders and emphasized the burden of disturbing symptoms of such diseases (‘*children have a really hard time with the scratching and pain*’). In the Netherlands,

participants did not report this scabies burden, possibly as a result of the scabies intervention program[10]. However, one of the participants indicated that not all of his clothes were returned after they were washed and he said that this had happened to others. Moreover, he had to stay in disposable overalls, while his clothes were being washed, as part of the intervention program for scabies and louse-borne relapsing fever[11] for longer than necessary, which he experienced as stigmatizing. 34 had no additional comments.

DISCUSSION

In this study, we aimed to investigate asylum seekers' perspectives on existing vaccination and screening policies in Greece and the Netherlands. We interviewed 61 asylum seekers originating from various different countries, mainly being Afghanistan and Syria. The majority of them described not having a negative experience with the screening and vaccination programmes and considered these policies of great importance for the well-being of asylum seeker population and public health.

In most European countries, vaccination policies for asylum seekers mainly focus on children[5]. However, several studies have shown low vaccination coverage among adult asylum seekers[12–14]. A Dutch study that included mostly asylum seekers from Syria, Iran, Iraq and Afghanistan showed insufficient protection against specific preventable diseases. Adults younger than 25 years showed the lowest measles seroprevalence[15]. In our study, the majority of participants underlined the defaults regarding adult vaccination and were open to supplementary vaccination. However, participants in the Netherlands were less supportive of further vaccinations. This difference could be explained by the different time points within the asylum seeking process. Greece functions as one of the transit countries while the Netherlands serves as a recipient country. Asylum seekers often have to face multiple health checks and experience different national vaccination policies throughout their journey. By the time they reach their final destination, their health care priorities may have changed.

Timely implementation of vaccination and screening policies is currently recommended by WHO and UNHCR[6,16]. A study from Sweden demonstrated awareness among asylum seekers regarding the benefits of timely screening, as participants expressed concern over the health risk posed by their living conditions and potential delay of screening appointment[17]. In accordance, in our study, the

majority of the participants preferred screening and vaccination policies to be implemented at point of entry in Europe. Participants expressed concerns regarding the increased risk of infectious diseases when people coming from different countries live closely together in centres and camps.

A systematic review on AMR among migrants in Europe demonstrated high prevalence of AMR carriage and AMR infection in migrants and concluded that implementing protocols for the prevention and control of AMR is necessary to ensure migrant health[18]. During the second part of the interview, asylum seekers were asked whether they had been admitted to a hospital, and if yes, whether they had been screened for MDROs. In Greece, as expected, none of the people that were admitted were screened for MDROs since there is no national MDRO screening policy regarding hospitalized asylum seekers. In the Netherlands, half of the asylum seekers that were admitted, reported they had been screened.

The majority of asylum seekers and children in need of additional vaccination or medical care, reported NGOs as the health provider, and such organisations were chosen as the preferred provider when asked. Political and social debate on which health provider is responsible for vaccination, screening and general medical care of asylum seekers, in European hosting countries, have led to an increased involvement of NGOs and volunteers in migrant health. NGO employees and volunteers do not necessarily have any special training or formal links with the national health-care system. Thus, linking NGOs with national healthcare systems in order to avoid discrepancies and optimize referral strategies could be challenging[19].

During the final part of the interview, asylum seekers were asked to give their perspectives regarding further screening on infectious diseases such as HIV and Hepatitis B and C. The majority of the participants were particularly concerned regarding STDs. Asylum seekers are often uneducated or misinformed regarding safe sexual practices and prevention of STDs[20,21].

The study was conducted in limited refugee camps and structures that we were granted access to, in Greece and the Netherlands. Subsequently, not all asylum seekers had the same probability to be included. Furthermore, distribution of demographic characteristics of the participants depended on the population composition at the time of the study. The number of invited participants depended on the documented feedback and interviews were carried out until data saturation was noted. Access to conduct the interviews in other asylum settings and in other time periods, may have yielded extra information. Another limitation of the study

was an increased ratio of men to women participants. Furthermore the number of participants originating from Sub-Saharan countries was small, leading to a possible gap in our results regarding their perspectives.

A strength of this study was the diversity of the study population regarding country of origin and educational level. Another strength was the different structures we visited in order to recruit the asylum seekers for the interview, an aspect that contributed to the diversity of the study population. Moreover, by conducting the study both in Greece and in the Netherlands, participants were at a different stage of their journey at the time of the interview. The interviews in Greece were conducted at an early stage of the asylum seekers' transnational journey while the interviews conducted in the Netherlands represent the perspectives of asylum seekers who are in the final stage of the asylum seeking process.

It has been proposed to implement screening and vaccination policies as a two parted action plan, with the first part mainly taking place at arrival in the temporary hosting country and the second part at their final recipient country[6,22]. A similar two-step has the potential plan to resolve the gap in vaccination among adult asylum seekers. Furthermore, alteration of screening policies in order to be in line with ECDC recommendations. Regarding STDs, existing screening policies for infectious diseases could be expanded in order to include screening for HIV, Hepatitis B and C. In our study, the need of vaccinations and screening was perceived lower amongst the participants in the Netherlands. Implementation of programs including vaccination and screening after reaching the asylum granting country may therefore be complicated by a switch in health care priorities of the asylum seekers.

Conclusions

To conclude, participants were willing to communicate their perspectives and concerns, and expressed a positive attitude towards vaccination and screening, understanding the rationale behind those policies for infection prevention and protection of public health. Our findings emphasize the need to include asylum seekers in the decision making of screening strategies. Based on the results, point of actions could be: (i) implementation of educational outreach programmes regarding screening, vaccination and safe sex practices, (ii) implementation of screening and vaccination programs will likely be more successful when the asylum seekers' need is perceived the highest, which is soon after arrival, (iii) include asylum seekers in the decision making on screening and vaccination strategies, (iiii) potential use of an open, easy to access online platform for communication between policy makers and asylum seekers that could provide valuable information.

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11

Summary

PART I – MULTIDRUG-RESISTANT ORGANISMS IN ASYLUM SEEKERS

In the beginning of 2014, little was known regarding the prevalence of multidrug-resistant organisms (MDROs) and infectious diseases in the migrant population. The increasing number of refugees trying to enter Europe and the subsequent healthcare needs of this vulnerable population challenged local healthcare systems. It was unclear which screening procedures for infectious diseases and MDRO colonization would be appropriate to meet the healthcare needs of asylum seekers, while at the same time protecting other vulnerable patients in the host country. Due to the expected high carriage rate of MDROs in asylum seekers in their country of origin, the department of Medical Microbiology and Infection Prevention of the University Medical Center Groningen (UMCG) advised screening for Methicillin-resistant *Staphylococcus aureus* (MRSA), Vancomycin-Resistant *Enterococcus* (VRE) and multidrug-resistant gram-negative bacteria (MDRGN) in April 2014. This advice was given to all asylum seekers who presented at the emergency department or were admitted to a hospital ward in the UMCG. After the general introduction of this thesis in **Chapter 1**, **Chapter 2** evaluates the carriage rate of MDROs seen in the asylum seeker patient population based on the screening as proposed by the department of Medical Microbiology and Infection Prevention. We report the infectious diseases detected in asylum seeker patients admitted to the UMCG, and a 31% prevalence of MDROs found among the asylum seeker patient population. This prevalence supports the screening strategies suggested earlier. The retrospective character of this study and the partially implemented protocol at the emergency department resulted in a 48% screening rate of all asylum seeker patients. This study setting was a tertiary hospital, no other health care facilities were included in this study which included only asylum seeker patients in need of specialized medical care. The prevalence reported here does therefore not necessarily reflect the general asylum seeker patient population.

In order to study the carriage rate of MDROs among the asylum seeker patient population in the Netherlands more closely, we conducted a second study (**Chapter 3**). The aim of this second study was to further assess the carriage rate of MRSA and multidrug-resistant Enterobacteriaceae (MDRE) among asylum seeker patients and compare these rates to the general patient population. The study was performed in collaboration with the laboratory of Certe. This laboratory performs microbiology diagnostics for all primary and hospital based healthcare facilities in the whole north-eastern region of the Netherlands. The samples analysed by Certe are obtained as part of standard care and include both clinical and screening samples

ranging from first to tertiary healthcare facilities. Since almost all asylum seekers start their asylum procedure at the national reception centre in Ter Apel, located in the north-eastern region of the Netherlands, asylum seekers in need of medical care are referred to one of the healthcare facilities in this area. Consequently, the samples analysed by Certe provide unique data to assess the carriage rate in the asylum seeker patients and the general patient population in the same area. We found a prevalence of 21% for MDRE (versus 5% in the Dutch reference population) and a prevalence of 10% for MRSA (versus 2% in the Dutch reference population) – a striking difference, again supporting the policy to screen for colonization of these high-risk pathogens. Although this study did not include the whole asylum seeker patient population, the data represents a more accurate sample of the asylum seeker patient population in the Netherlands compared to the data in **Chapter 2**. This data provides important and highly relevant information advocating screening precautions. It must be noted that the MDRO prevalence presented in **Chapters 2** and **3** does not necessarily reflect the MDRO prevalence in the asylum seeker population as a whole, but reflects the prevalence of MDROs among asylum seeker patients, as MDRO carriers are more prone to infection. These patients report to healthcare facilities sooner and more often compared to non MDRO carriers. Furthermore, sources of potential bias, e.g. bias by indication, as the data in **Chapter 3** also contained clinical samples taken in case of a suspected infection, influence the data leading to a probable higher prevalence observed among the asylum seeker patients compared to the asylum seeker population.

The mere presence of these organisms on entry is alarming and emphasizes the need for subsequent screening precautions. However, if asylum seekers lose their MDRO quickly after arrival in the Netherlands, these precautions only need to be applied for a certain number of months after arrival. In general, the duration of MDRO colonization in humans is variable and humans may lose their MDRO over time, as has been shown to occur after international travel. Screening and subsequent isolation precautions in hospitalised asylum seekers comes at a price; both for patients that may be less effectively monitored, apart from experiencing loneliness, depression and even stigma, as for the healthcare system, as with isolation, more staff and space are required. If asylum seekers lose their MDRO over time, as happens to international travellers, precautions only need to be taken during a limited number of months after arrival in the Netherlands. This will lead to more targeted screening and isolation strategies and reduction in adverse effects associated with isolation precautions. Based on this theory of possible temporary MDRO prevalence, we studied the carriage rate of MDROs in asylum seeker patients over time (**Chapter 4**). Data from 2,091 samples of asylum seekers

admitted to the hospital was retrospectively collected. The rates of MRSA and MDRE detected were calculated after arrival in the Netherlands. Unexpectedly, the typical pattern of decline over time, as reported after international travel, was not observed. More targeted screening strategies for asylum seekers could therefore not be recommended.

Apart from the duration of carriage of MDROs in the asylum seeker population, microbial analysis and outbreak investigation may reveal valuable information for the development of more targeted screening guidelines and potential spread of MDROs in this population. Whole genome sequencing has become a useful tool for providing information on detection, identification, resistance profile genotype, epidemiological typing, and genetic and phylogenetic relatedness amongst different strains. In **Chapter 5**, we sequenced 112 ESBL-*E. coli* isolates from asylum seekers. These strains were compared to 52 sequenced ESBL-*E. coli* strains from hospitalized patients in the Netherlands and Germany. The 52 isolated were used as context isolates in the genomic comparisons with the isolates from asylum seekers. A large variability in both phenotypic and genotypic resistance and phylogenetic relatedness was observed among asylum seekers originating from the same country of origin. Although formation of small clusters within the asylum seeker population was found, no obvious patterns of transmissions within this population could be identified. The duration and dynamics of colonization of these high-risk pathogens appeared highly complex; clearly more studies are needed to explore the duration and dynamics of colonization of high-risk pathogenic bacteria among international migrant populations, seeking asylum in the Netherlands and other affluent countries in Europe - and beyond.

PART II – SCREENING AND VACCINATION

The second part of this thesis focuses on the evaluation of screening and vaccination programs in the Netherlands and Europe. In 2015, the national reception centre for asylum seekers in Ter Apel noticed an increase of scabies cases among asylum seekers originating from Ethiopia and Eritrea. Therefore, the primary health care centre (GCA), located at the national reception centre, introduced a preventive screening programme using mass drug administration (MDA) at the national reception centre Ter Apel in July 2015. Ethiopian and Eritrean asylum seekers were actively screened and treated for scabies or given ivermectin or permethrin as a preventive treatment in order to control the scabies outbreak. **Chapter 6** is dedicated to this screening programme and aims to evaluate the treatment outcome of all who received (preventive) scabies treatment. The medical records of 2,866 asylum

seekers were followed over time of which 532 asylum seekers were included before the start and 2,334 asylum seekers were included after the start of the programme. Data was extracted from the medical records such as clinical scabies manifestation, complication, treatment given, and repeated use of ivermectin or permethrin. The GCA uses a centralized electronic health care system for all asylum seekers in the Netherlands that allows for an accurate follow up on asylum seekers and their treatment outcomes, even if asylum seekers have been referred to other asylum seekers centres in the Netherlands. We found that 897 (38.4%) of the 2,334 asylum seekers who received ivermectin or permethrin during the programme had clinical signs of scabies and of these 897 asylum seekers, 580 (65%) were diagnosed with scabies on arrival. The percentage of new scabies episodes declined from 42% to 27% and the percentage of complications declined from 12% to 5% as a result of the programme. Hence, the programme was considered feasible and effective in terms of an early diagnosis of the patients, a reduction of the number of re-infestations, and complications. Although this was a retrospective cohort study with pre- and post-interventional data collection and inherent methodological weakness, it is the first and only study available showing the positive effect of a preventive screening programme with MDA in the asylum seeker population. MDA is an essential tool to reduce the burden of highly contagious diseases and to contain outbreaks of such diseases - especially in crowded settings such as the national reception centre of Ter Apel or other refugee settings as also emphasized in **Chapter 7**.

In addition to screening programmes and mass drug administration, vaccination is another relevant tool to reduce the burden of infectious diseases in asylum seekers. **Chapter 8** examines current vaccination policies implemented across Europe. Vaccination policies were obtained by contacting national vaccination experts of all 32 European Union/European Economic Area (EU/EEA) countries and Switzerland. They were asked to provide (national) vaccination documents for their country. Moreover, a systematic literature search was carried out to complete the experts' input and all data was analysed using framework analysis. A considerable variation in policies across Europe regarding the approaches in vaccination, especially in child and adult vaccinations, was found. Only six countries had comprehensive guiding policies on the vaccination of migrants; four countries focused on both adults and children and two focused on children only. Most countries (60%) use their national vaccination schedule for vaccination of migrants. In ten countries, policies focussed only on priority vaccinations with different priority vaccinations identified across the different age groups.

To further explore vaccination approaches and to provide more insight into optimal and preferred vaccination strategies across Europe, we invited 32 national vaccination experts who were all working for the Ministry of Health or in the field of public health, to complete a questionnaire on their priorities and recommendations in the field of migrant vaccination (**Chapter 9**). These experts reported that more clarity is needed on which vaccinations should be prioritized and that strategies or guidance for catch up vaccination are needed. They recommended providing vaccinations in multiple settings, e.g. at the point of entry and holding level/reception centres, and to be free of charge. Both these results and the results of **Chapter 8**, clearly show the diversity in migrant vaccination across Europe and the need for clarity on optimum vaccination strategies in this population.

The organisation and implementation of screening and/or vaccination activities is frequently debated. Besides the perspectives of vaccination experts, as was discussed in **Chapter 9**, the perspectives of (former) asylum seekers may be helpful to provide more insight into the implementation of screening and/or vaccination activities and consequently contribute to the compliance to such policies. In **Chapter 10** we assessed the perspectives of asylum seekers on infectious diseases screening and vaccination policies. In total, sixty-one asylum seekers were interviewed in Greece and in the Netherlands in order to include asylum seekers that are at different stages of the asylum seeking procedure. Overall, the interviewed asylum seekers consider vaccination policies of great importance in order to promote their own well-being, as well as the public health in general in the host country. A positive attitude towards vaccination and screening was expressed by the participants. Interestingly, participants in the Netherlands were less supportive and open to further vaccination compared to participants in Greece. Considering the multiple health checks and experience with different national vaccination policies throughout their journey in Europe, it is likely that their health care priorities have changed. The study was conducted in one setting in Greece and in one setting in the Netherlands leading to a selection bias in the study population since not all asylum seekers had the same probability to be included in the study. Moreover, demographic data of the participants depended on the population in the centres, subsequently Sub-Saharan nationalities in this study were only partly represented. Nevertheless, these findings demonstrate a general positive attitude towards screening and vaccination programs. Screening and vaccination programmes can be more effectively implemented when asylum seekers and refugees are involved in the development of such policies.

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Discussion and future perspectives

PART I – MULTIDRUG-RESISTANT ORGANISMS IN ASYLUM SEEKERS

The discovery of penicillin by Sir Alexander Fleming in 1928 marked a new era for the treatment of bacterial infections. Penicillin was officially introduced as a commercialized antibiotic in 1943[1,2]. In 1945, Sir Fleming, who won the Nobel Prize for his discovery the same year, already warned of the misuse or overuse of penicillin that could lead to the selection of bacteria and possible resistance. Shortly after penicillin was introduced, the first cases of resistance were reported[3]. Despite the development and the introduction of new antimicrobial groups, micro-organisms nowadays have developed resistance mechanisms for almost all of these antimicrobial groups, leaving clinicians with limited treatment options[4]. The European Centre for Disease Prevention and Control (ECDC) defines multidrug-resistant organisms (MDROs) as organisms that are resistant to one or more agents in at least three or more antimicrobial groups[5]. Antimicrobial resistance (AMR) has become one of the most considerable challenges in public health worldwide. Indeed, AMR threatens the effective prevention and treatment of common bacterial infections such as pneumonia, urinary tract infections, and tuberculosis[6,7]. AMR is associated with increased morbidity, a higher number of re-admissions, an increased number of hospitalisation days, and an increased mortality rate[8,9] resulting in a heavy global economic burden due to the higher treatment costs and reduced productivity caused by illness. As a result of AMR, the costs for the European Union (EU) are estimated to be 1.5 billion euro per year. Moreover, an estimated number of 25 000 deaths in the EU are reported annually as a result of resistant bacteria[6,10].

Epidemiology of MDROs in asylum seekers

With the increasing number of refugees entering Europe in the beginning of 2014, a fear for the introduction of MDROs developed because of a suspected higher MDRO prevalence in their country of origin. Crowded conditions during their transit to Europe might facilitate transmission and enhance carriage; and in community settings such as asylum seekers centres or detention facilities, the carriage of MDROs in this population would be further enhanced. Since 2014, various studies have been conducted on the prevalence of MDROs in asylum seekers. These studies, as well as the studies presented in **Chapters 2** and **3** of this thesis, showed a high prevalence of MDROs among the asylum seeker patient population[11–16]. However, the prevalence reported in these studies varies. A systematic review of AMR among migrants in Europe showed a pooled prevalence of 25.4% (95% CI 19.11–31.8) for MDRO. The prevalence of methicillin-resistant *Staphylococcus*

aureus (MRSA) was 7.8% (95% CI 4.8–10.7); and carriage of antibiotic resistant Gram-negative bacteria (MDRGN) was 27.2% (95% CI 17.6–36.8)[17]. A German study, published in 2016, showed a MDRGN carriage rate of 61% patients in a university hospital. This is almost triple the number as reported in **Chapter 3**[12]. The difference in study population of the two studies could be an explanation for this variation in the MDRO prevalence. The German study only included patients in tertiary care facilities. These patients may have higher MDRO carriage rates than the patients attending first and second line care as described in **Chapter 3**. Other explanations for the difference in MDRO carriage could be the difference in travel route and the difference in the epidemiology in the country of origin, transit countries and in the host country. Furthermore, (previous) antibiotic pressure or different definitions used for MDROs across the various studies could be an explanation. Despite these reported differences in MDRO prevalence, the various studies show the need for MDRO screening strategies upon admission - especially in countries with a (relatively) low MDRO prevalence such as the Netherlands. These strategies are needed to enable optimal treatment of asylum seeker patients and optimal strategies in infection control in the hospital.

Screening strategies for MDROs and implementation

Spontaneous clearance of MDRO carriage among travellers returning from international travels to high prevalence countries has been observed before[18,19]. For example, 83% of the international travellers that initially tested positive for Extended-Spectrum Beta-Lactamase (ESBL)-Enterobacteriaceae after their return to the Netherlands, tested negative six months later[18]. Based on this information, the same pattern of decline was expected in the asylum seeker population, but surprisingly, this clear pattern of decline was not observed (**Chapter 4**). Another German study showed that the prevalence of MDRGN and MRSA in refugees eventually declined, but only eighteen months after arrival in Germany[20]. Different clearance rates of MDRO carriage observed in travellers and migrants could be explained by differences in the microbiome of both groups. Migrants might have a well-established MDRO within their microbiome due to a higher microbial load in their country of origin, while travellers acquire their MDRO carrier state during their journey. The travellers were not colonized prior to traveling and therefore lost their MDRO more easily after coming home. The microbiome of people who move from a non-Western country to a Western country gradually changes and the native microbiome is lost[21]. This change is partly explained by diet, but also by other factors such as drinking water and antimicrobial use. Travellers returning from international travel will revert back to their familiar living and diet habits, whereas asylum seekers

living in centres will most likely hold on to their original habits, which, besides other factors, may contribute to the slow change in their microbiome and thus prolong the elimination of their MDRO.

A second reason for the prolonged carriage of MDROs in this population could be crowded living conditions of centres where asylum seekers are staying leading to MDRO transmission. Clearance of MDRO carriage might be observed when they are granted asylum and no longer live in such conditions. To confirm this hypothesis, transmission or cluster formation observed within refugee centres or settlements would provide a solid argument for the transmission of MDROs among refugees, and would explain possible prolonged carriage of MDROs. With the introduction of whole genome sequencing (WGS), this can now be investigated[22]. WGS of Gram-negative bacteria of asylum seeker patients showed, however, no clear pattern of the transmission of Gram-negative bacteria (**Chapter 5**). It should be born in mind that these samples were obtained retrospectively. Although our study showed sporadic clusters of transmission; it cannot be ruled out that larger clusters would have been detected if more samples would have been included from refugees with closer epidemiological links. Other studies reporting on sequence data in samples from refugees are scarce. In an Italian study, phylogenetic analysis of ESBL-*Klebsiella pneumonia* from a Syrian refugee showed no clustering with any Italian strains[23]. The same conclusion was drawn based on a German study, where WGS revealed no definitive transmission among refugee patients as long as standard hygiene measures are applied[24].

Ways forward

The indication for screening policies for MDROs in the Netherlands is obvious, and is therefore recommended. The current scientific background showed that the carriage of MDROs in asylum seekers is most likely prolonged compared to travellers. However, we can only speculate why carriage of MDROs in refugees is prolonged, since no clear answers have yet been found. Screening policies applied to asylum seekers should be continued for a longer time period than screening policies applied to international travellers. Based on the findings in this thesis, the department of Medical Microbiology and Infection Prevention recommended screening policies for refugees and asylum seekers up to 3 years after arrival in the Netherlands. In the future, a prospective, longitudinal cohort study is needed to design targeted screening strategies. During such a cohort study, recently arrived asylum seekers should be screened for MDROs shortly after arrival in the Netherlands. This screening should be continued up to three years after arrival. The

vulnerability of this group, especially shortly after arrival in the Netherlands, requires an ethically and culturally sensitive approach to conduct this study. The ideas and perspectives of (former) asylum seekers could be helpful and should be taken into account while designing this study. Besides longitudinal testing for MDROs in this population, more insight is needed into health behaviour of migrants after arrival in the host countries. The Lifelines database, which is a large multigenerational cohort in the northern region of the Netherlands, contains data of 167.000 participants, including migrants, and provides unique data regarding health behaviour of migrants after arrival in the host country[25]. Future study of this database will contribute to the knowledge of a possible change in antibiotic consumption. This information is needed to better understand MDRO carriage in the migrant population.

PART II - SCREENING FOR COMMUNICABLE DISEASES AND VACCINATION

The potential of mass drug administration in scabies

In general, asylum seekers originate from countries with a relatively high prevalence of infectious diseases. The overall perception and fear across Europe for the introduction of infectious diseases in the host countries due to migration is understandable, yet unwarranted. The World Health Organisation (WHO) reported no systematic correlation between the importation of infectious diseases in the host country and migration[26]. The vulnerability of the asylum seeker population to communicable diseases is, however, increased due to the limited access to health care in their country of origin. We also observed that half of the asylum seekers admitted to the UMCG presented with an infectious condition such as tuberculosis and *P. vivax* malaria. Moreover, infectious diseases that are less common, such as leishmaniasis or louse borne relapsing fever were observed, demonstrating the vulnerability of this population (**Chapter 2**). Therefore, health care for migrants should not only focus on the fear for the importation of infectious diseases and the possible public health threat in the host countries, but specifically on the best practices in migrant health to reduce the burden of communicable diseases in this group. A representative example of a best practice in migrant health is the scabies intervention programme that was implemented at the national reception centre in Ter Apel, the Netherlands in July 2015. This mass drug administration (MDA) programme with ivermectin led to a reduction of the burden of scabies in the centre (**Chapter 6**). Scabies outbreaks have been reported in crowded settings such as refugee camps or settlements in recent years[27]. MDA proved to be an adequate tool to reduce the burden of communicable diseases in such settings and should

be integrated into screening programmes in the future[28]. MDA is already indicated if the prevalence of scabies is more than 10%[29]. It is the preferred and only effective method to contain scabies outbreaks on a large scale, as was also recently reported during an outbreak in northern Ghana. Passive case finding was initially done to contain the outbreak, but turned out to be ineffective to treat all scabies cases (Amaoko Y, submitted).

Knowledge of the implementation of MDA in such settings is urgently needed and should be a point of action in the future. Prospective data is needed to determine the MDA threshold, which drugs should be administered, and the number of times that drugs should be administered[28]. So far, various MDA-programmes with oral ivermectin proved to be successful[30–33] and ivermectin is most likely the preferred agent for such interventions. Topical treatments have several disadvantages, including strict instructions for the application of the agent, severe adverse effects such as skin irritation, and distress for the patient. These disadvantages will lead to a poorer compliance in the use of topical agents, especially on a larger scale. Oral ivermectin is easy to administer and is therefore more feasible compared to topical treatments[34,35]. In addition, ivermectin has shown to have the same efficacy as permethrin, especially if a second round ivermectin is administered [36]. Since ivermectin does not kill scabies eggs, this second dose is needed to kill newly hatched larvae from the remaining eggs, but a second dose will also challenge adherence to this intervention[37,38]. Newly developed agents such as slow release ivermectin would be more practical, and possibilities for the use of such agents should be investigated in future research activities. Effective communication between different asylum seekers centres or settlements during these interventions is crucial. Platforms for communication could help to raise awareness for programmes like the scabies programme in Ter Apel, and will help with the rapid implementation of screening programmes if needed.

Challenges in the vaccination of migrants

A second approach to reduce the burden of communicable disease is to guarantee adequate immunization rates among migrants. Insufficient vaccination rates for vaccine-preventable diseases such as measles have been reported among migrants[39–42]. A European level intervention is required to optimize immunization levels among migrants. However, the question remains how to do so. The ECDC guideline, published in 2018, recommends vaccinating recently arrived migrants according to the national vaccination schedule of the host country with priority for vaccination of mumps, measles, rubella, diphtheria, tetanus, pertussis,

polio, *Haemophilus influenza* type b, and hepatitis B[43]. This recommendation is informative and can be applied in practice after a migrant has arrived in the host country. However, many migrants are on the move, and the organisation of vaccination of these migrants remains a huge challenge, especially considering the differences in health services and registration of vaccination across Europe. These differences complicate cross-border collaboration and could result in over and/or under immunisation of migrants[44]. Although a uniform European registration system for the documentation of vaccination across Europe would be ideal, such a system is currently not feasible. Instead, an alternative option for the registration of vaccinations in migrants across different European countries could be the use of a mobile application. This system would facilitate the registration of vaccination by migrants themselves and might be a helpful tool to gain more insight into the vaccination status of migrants. Although this could be a possible solution, in the end, the vaccination of migrants remains a political responsibility. As a result, the vaccination of migrants has to be organised on a (inter)national level. A renewed political view is needed to provide access to safe, effective, quality and affordable vaccines for all[45].

The perspectives of migrants on the development of screening and vaccination policies improves adherence and willingness to collaborate in such policies, contributing to the reciprocity principle of screening programmes[46]. Overall, migrants are willing to participate in screening and vaccination policies (**Chapter 9**) and politicians could use this willingness to promote migrant health. Interviewed asylum seekers suggested an open, easy to access online platform for communication between policy makers and asylum seekers, to investigate international needs and promote collaboration. The use of an online platform or social media could be a valuable tool for further research. Compliance, participation but also shortfalls in current screening and vaccination policies should be addressed in future research activities with the help of such platforms.

Migrant Health in times of the COVID-19 pandemic

At the time of completing the writing of this thesis, the world witnessed an unprecedented global pandemic with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also known as the coronavirus disease 2019 (COVID-19)[47,48]. This COVID-19 pandemic has posed an enormous burden on health systems worldwide. Clearly, the focus has predominantly been on the impact on health care systems in affluent parts of the world and the subsequent (public health)

measures that had to be taken[49–51]. However, the impact of COVID-19 in low- and middle-income countries with weaker health care systems and weaker reporting systems in place is probably even more daunting[52,53].

The COVID-19 pandemic that originally began in the last weeks of 2019 in a local food market in Hubei province[54], inland China rapidly spread by air travel to almost all parts of the world[55]. This pandemic illustrates how the world has become connected nowadays and how relevant the topics are that we discussed in this thesis. Indeed, migration medicine is now prime time and an international collaboration and open political attitude of governments is required to guarantee and protect the health of the most vulnerable of society, especially in times like these. Meanwhile, the economic hardships and health care restraints incurred by the pandemic driven governments, individual politicians, and opinion makers result in the contrary; an even more restrictive border control, and a less permissive attitude towards ill health of asylum seekers, refugees, and immigrants[56,57]. Unfortunately, their suffering received less attention than warranted in a crisis like we are facing today[58,59]. As an example, refugees and asylum seekers have faced extreme hardships while waiting for their immigrant screening procedures at the borders of the European, Asian and American territories[60–62]. Besides these extreme hardships regarding immigrant screening procedures, many of them live in facilities that are overcrowded and lack the basic public health measures such as proper sanitation, posing a great risk of infections for the residents of such facilities, and therefore pose a public health threat[56,63]. As governments tend to tighten their policies towards refugees and migrants in times of crisis such as this COVID-19 crisis, they should realize that (public health) efforts will only be effective and successful if guided by an inclusive approach to all, including refugees and migrants[64]. To conclude, this current pandemic crisis brings to light what this thesis is about, as was also nicely stated by Kluge and colleagues; ‘there can be no public health without refugee and migrant health’[56].

Ways forward

The on-going political and social debate on who is responsible for migrant health, how to implement guidelines, and, most importantly, the restrictive health and social policies in host countries across the EU/EEA are all hurdles in providing health care to this vulnerable population[45]. To date, no international consensus on how to organise migrant health has yet been reached. Although presently the number of refugees trying to enter Europe is relatively low compared to 2015, and the political debate about migration and health care for migrants has calmed

down, migration remains a phenomenon of all times. In this thesis, we reported on the burden of communicable diseases, showed best practices to reduce the burden of communicable diseases, and analysed current vaccination policies that will hopefully contribute to improve migrant health. Non-communicable diseases did not fall under the scope of the thesis. However, clearly, non-communicable diseases, especially mental health problems, are important, and should therefore be addressed in the context of migrant health[65,66].

Meanwhile, medical doctors and local health care systems cannot wait for a politically correct consensus, and have their unique role to play in the promotion of migrant health and in the social integration of migrants, in accordance with their professional competence to address their societal role as health advocates[67,68]. As medical professionals are often consulted by migrants and refugees for help and advice, they serve as a gateway to other social services leading to further integration of migrants into society. Active promotion and protection of migrant health will contribute to achieve the health related sustainable development goal 3 '*good health and well-begin for all*' of the host countries[69,70] and hopefully help to meet the needs of the migrant population in the future.

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13

Nederlandse samenvatting

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NEDERLANDSE SAMENVATTING

Hieronder volgt een Nederlandse samenvatting voor de leek.

Deel I – Bijzonder resistente micro-organismen bij asielzoekers

Door de aanhoudende onrust in het Midden-Oosten, maar ook in andere gebieden in Azië en Afrika, werden de afgelopen jaren veel mensen gedwongen hun land te verlaten. De United Nations High Commissioner for Refugees (UNHCR), de vluchtelingenorganisatie van de Verenigde Naties, schat dat wereldwijd per jaar ongeveer 40 miljoen mensen gedwongen moeten vluchten. Dit aantal is de afgelopen jaren echter aanzienlijk toegenomen met de hoogste piek geobserveerd in 2015. Wereldwijd sloegen dat jaar meer dan 65 miljoen mensen op de vlucht, waarvan één miljoen mensen Europa probeerden te bereiken. De meeste vluchtelingen kwamen uit Syrië en Afghanistan.

Gezien de kwetsbare situatie van veel vluchtelingen en de beperkte toegang tot gezondheidszorg werd gedacht dat vluchtelingen mogelijk meer vatbaar zouden zijn voor infectieziekten. Daarnaast was de verwachting dat bijzonder resistente micro-organismen (BRMO's) of bepaalde infectieziekten zoals tuberculose gevolgen zouden kunnen hebben voor de bevolking van het land waar vluchtelingen heen vluchten. BRMO's zijn bacteriën die resistent zijn voor één antibioticum of meer antibiotica in drie of meer verschillende groepen antibiotica. Bekende voorbeelden zijn Methicilline-resistente *Staphylococcus aureus* (MRSA) of Extended Spectrum Beta-Lactamase (ESBL)- producerende *Escherichia coli* (*E. coli*). Als een patiënt besmet is met een BRMO is het daardoor moeilijker om een zieke patiënt te behandelen met antibiotica. Dit kan gevolg hebben voor de uitkomst van de ziekte. Het percentage BRMO's in de Nederlandse ziekenhuizen is heel laag. Dit komt onder andere door het relatief lage antibiotica gebruik in de Nederlandse gezondheidszorg. Daarnaast worden mensen die een verhoogd risico hebben op het dragen van een BRMO gescreend op een BRMO bij opname in een ziekenhuis. Indien noodzakelijk worden isolatiemaatregelen genomen om verdere verspreiding te voorkomen.

Het eerste deel van dit proefschrift gaat over BRMO's bij asielzoeker patiënten. Het is bekend dat reizen en migratie een risicofactor kunnen zijn voor het verspreiden van BRMO's en infectieziekten. Mogelijke inbreng van BRMO's en infectieziekten door asielzoekers zou een invloed kunnen hebben op het beleid dat gevoerd wordt in ziekenhuizen. In het begin van 2014 was er nog weinig bekend over het percentage (de prevalentie) BRMO's bij asielzoekers. De inschatting van de afdeling

Medische Microbiologie en Infectiepreventie van het Universitair Medisch Centrum Groningen (UMCG) was dat de prevalentie van BRMO's onder asielzoeker patiënten hoger zou zijn in verhouding tot de Nederlandse patiëntenpopulatie. Daarom werd geadviseerd om alle asielzoekers die in het UMCG moesten worden opgenomen te screenen op BRMO's. Na de algemene inleiding van dit proefschrift in **hoofdstuk 1**, onderzoeken we in **hoofdstuk 2** de prevalentie BRMO's bij asielzoeker patiënten. Dit hebben we gedaan door te kijken naar de screeningsresultaten van asielzoekers die zijn opgenomen in het UMCG en gescreend zijn op een BRMO zoals geadviseerd door de afdeling Medische Microbiologie en Infectiepreventie. We vonden dat 31% van hen één of meerdere BRMO's bij zich droegen. Deze prevalentie is veel hoger dan in de algemene patiëntenpopulatie in Nederland. Deze studie werd echter alleen maar in een universitair ziekenhuis uitgevoerd waar veel mensen behandeld worden die gespecialiseerde zorg nodig hebben. Om de prevalentie van BRMO's bij asielzoeker patiënten beter in kaart te brengen, hebben we in **hoofdstuk 3** gekeken naar de prevalentie van BRMO's in de patiëntenpopulatie in heel Noordoost Nederland. In deze studie hebben we zowel gekeken naar de prevalentie van BRMO's van asielzoeker patiënten, maar ook naar de prevalentie van de andere patiënten. Hierdoor konden we het percentage van de twee groepen met elkaar vergelijken. Opnieuw vonden we dat er een hoger percentage was voor BRMO's bij de asielzoeker patiënten in verhouding tot de andere patiënten. Met deze resultaten, en ook andere studies die rond die tijd zijn gepubliceerd, kunnen we concluderen dat de prevalentie van BRMO's bij asielzoeker patiënten hoger is dan in de algemene patiëntenpopulatie. Het toepassen van screeningsmaatregelen bij opname in het ziekenhuis voor BRMO's voor asielzoekers is daarmee geïndiceerd. Echter, de volgende vraag die beantwoord moest worden is hoelang deze screeningmaatregelen dan moeten worden toegepast. Het is bekend dat reizigers die terugkomen van een internationale reis en een BRMO bij zich dragen, deze BRMO na ongeveer 6 maanden weer kwijt zijn. Als dit ook voor asielzoekers zou gelden, zouden screeningmaatregelen 6 maanden na aankomst in Nederland opgeheven kunnen worden. In **hoofdstuk 4** hebben we gekeken hoelang asielzoekers na aankomst in Nederland nog een BRMO bij zich droegen. Hier vonden we echter geen duidelijk patroon van afname in en lijkt het zo te zijn dat asielzoekers een BRMO langer bij zich dragen dan reizigers dit doen na terugkomst in Nederland.

Om meer duidelijkheid te krijgen over het dragerschap van BRMO's hebben we in **hoofdstuk 5** gekeken naar de genetische code - het hele DNA van BRMO's, ook wel een genoom genaamd. Dit hebben we gedaan door middel van Whole Genome Sequencing. Dit is een techniek waarbij het DNA van een bacterie tot in detail wordt bestudeerd (sequencing). Op die manier kan gekeken worden of bacteriën aan

elkaar verwant zijn. Mochten er verwante bacteriën bij verschillende patiënten gevonden worden, dan zou dit kunnen betekenen dat BRMO's aan elkaar worden overgedragen of dat er wellicht een uitbraak geweest is in een asielzoekerscentrum. We hebben één soort BRMO (ESBL- producerende *E. coli*), van asielzoekers die in 2016 waren opgenomen in het ziekenhuis, gesequenced. Hoewel we een aantal ESBL-producerende *E. coli*'s vonden die aan elkaar verwant waren, konden we geen duidelijk patroon van overdracht vinden. Er kon dus op basis van deze studie niet geconcludeerd worden dat ESBL-*E. coli*'s onder asielzoekers overgedragen worden. Het blijft daarom onduidelijk hoelang deze screeningmaatregelen daadwerkelijk moeten worden toepast. Om dit te onderzoeken, zou een onderzoek opgezet moeten worden waarbij asielzoekers vanaf de dag van aankomst in Nederland tot drie jaar na aankomst getest worden op het dragen van een BRMO. Op deze manier kan er gekeken worden of het percentage BRMO's afneemt in de loop van de tijd of niet.

Deel II – Screening en vaccinatie

In het tweede deel van dit proefschrift proberen we huidige richtlijnen voor de screening op infectieziekten en vaccinaties in kaart te brengen en te evalueren. In 2015 merkten de medewerkers van het aanmeldcentrum voor asielzoekers in Ter Apel dat er een toename was van het aantal asielzoekers met klachten van schurft. Deze asielzoekers kwamen met name uit Eritrea en Ethiopië. Schurft is een parasitaire ziekte die zorgt voor veel jeukklachten en via de kapot gekrabde huid kunnen ook bacteriën de huid binnen dringen: we spreken van secundaire bacteriële infecties. Het is een zeer besmettelijke ziekte waarbij zowel de patiënt behandeld moet worden, als ook de mensen die met de patiënt in contact zijn geweest om verdere verspreiding te voorkomen. Gezien de krappe huisvesting en de drukte in het aanmeldcentrum in Ter Apel werd door het medische team aldaar besloten dat er een indicatie was om een preventief programma op te zetten. Alle asielzoekers uit Eritrea en Ethiopië werden bij aankomst in het aanmeldcentrum onderzocht op mogelijke klachten van schurft. Daarnaast werden tegelijkertijd de kleren gewassen die zij droegen bij aankomst in het aanmeldcentrum. Indien bij iemand schurft gediagnostiseerd werd, werd dit behandeld. Als iemand geen schurftklachten had, werd er eenmalig medicatie ter preventie van schurft gegeven. In **hoofdstuk 6** hebben we dit programma geëvalueerd. Het programma bleek effectief te zijn in het vroegtijdig diagnosticeren van schurft. Daarnaast nam het aantal complicaties als gevolg van schurft af en kwam schurft ook minder vaak terug bij de asielzoekers die in eerste instantie met schurft gediagnosticeerd waren. Een preventief programma zoals het schurftprogramma kan een oplossing zijn voor

het behandelen van besmettelijke ziekten op locaties zoals vluchtelingencentra. Dit zou een toegevoegde waarde zijn voor huidige screeningprogramma's zoals ook besproken is in **hoofdstuk 7**.

Naast preventieve screeningprogramma's is vaccinatie ook een zeer nuttige manier om infectieziekten te voorkomen. Het is bekend dat de vaccinatiegraad onder vluchtelingen niet altijd voldoende is. Dit komt onder andere doordat zij gedurende langere tijd onvoldoende toegang tot gezondheidszorg hadden en daarmee ook niet tot de vaccinatieprogramma's in hun land van herkomst. Een lagere vaccinatiegraad onder vluchtelingen maakt deze groep meer vatbaar voor infectieziekten. Er ligt daarom een belangrijke taak voor Europa om te zorgen dat asielzoekers de juiste vaccinaties krijgen om op deze manier de vaccinatiegraad van deze groep te garanderen. Echter, vaccinatieprogramma's in de Europese landen verschillen. Gezien het feit dat vluchtelingen gedurende hun vlucht naar Europa door verschillende landen reizen, is het regelen van vaccinaties voor vluchtelingen lastig en is er tot op heden nog geen consensus bereikt hoe dit geregeld moet worden. Om meer inzicht te krijgen in de verschillende vaccinatieprogramma's voor vluchtelingen in alle 32 Europese landen hebben we in **hoofdstuk 8** een analyse gedaan van het beleid van alle Europese landen omtrent vaccinatie. Daarnaast hebben we in **hoofdstuk 9** aan experts op het gebied van vaccinatie gevraagd wat zij belangrijke punten van aandacht vinden. We vonden dat er een aanzienlijke variabiliteit is binnen het beleid van de Europese landen voor het vaccineren van migranten. Daarbij wordt er vaak ook nog een ander beleid gevoerd voor kinderen en volwassenen. Er zijn zes landen die een richtlijn hebben specifiek gericht op vaccinatie van migranten, waarvan twee van deze zes landen alleen focussen op de vaccinatie van kinderen. De meeste landen (60%) gebruiken het vaccinatieschema van het eigen land voor het vaccineren van migranten. De vaccinatie-experts adviseren om vaccinatie te richten op zowel kinderen, als volwassenen. Bovendien vinden zij het belangrijk dat vaccinatie op verschillende momenten in het migratieproces gegeven moeten worden, bijvoorbeeld bij binnenkomst in het land, of bij aankomst in een aanmeldcentra.

Om richtlijnen uiteindelijk goed te kunnen implementeren is het van belang om rekening te houden met de ideeën van asielzoekers zelf. Hiermee wordt de bereidheid vanuit asielzoekers om mee te doen aan screeningsprogramma's ook vergroot. In **hoofdstuk 10** hebben we daarom 61 asielzoekers geïnterviewd. We vroegen hun mening over screening en vaccinatie en wat verbeterd kan worden. Dit hebben we gedaan in Griekenland en Nederland. Over het algemeen zagen de deelnemers het belang in van een vaccinatiebeleid en het screenen

op infectieziekten. Zij vonden dit belangrijk om zowel hun eigen gezondheid te verbeteren en de gezondheid van de bevolking van het land waar zij verblijven te beschermen tegen infectieziekten.

Migrantengezondheid gedurende de COVID-19 pandemie

Gedurende het schrijven en afronden van dit proefschrift is er sprake van de pandemie met het nieuwe coronavirus SARS-CoV-2 dat de ziekte COVID-19 veroorzaakt. Deze pandemie zorgt voor een enorme druk op zorgsystemen wereldwijd. De COVID-19 pandemie begon in de laatste weken van 2019 op een lokale voedselmarkt in de provincie Hubei, China en heeft zich snel verspreid over de wereld. Deze pandemie laat zien hoe de wereld tegenwoordig met elkaar verbonden is en hoe relevant de onderwerpen zoals besproken in dit proefschrift zijn. Migrantengezondheid is van groot belang. Internationale samenwerking en een open politieke houding van overheden is nodig om de gezondheid van de meest kwetsbare van de samenleving, zoals migranten, te garanderen en beschermen, zeker in tijden zoals deze. Echter gebeurt er in tijden van crisis vaak het tegenovergestelde; een strenger grensbeleid en een minder toegeeflijke houding tegenover asielzoekers, vluchtelingen en immigranten. Naast dit strengere beleid leven velen van hen in faciliteiten die overbevolkt zijn met een gebrek aan basisbehoeften zoals goede sanitaire voorzieningen. Dit leidt tot een toegenomen risico op infecties voor de bewoners van deze faciliteiten en dit kan daarom een bron zijn voor nieuwe uitbraken. Hoewel overheden de neiging hebben om hun beleid te verscherpen ten opzichte van vluchtelingen en migranten in tijden van crisis, zoals deze COVID-19 pandemie, moeten ze zich realiseren dat pogingen voor het promoten van de volksgezondheid van het land alleen effectief en succesvol zullen zijn als zij die doen vanuit de gedachte dat iedereen wordt meegenomen, inclusief vluchtelingen en migranten.

Toekomstperspectief

Het aanhoudende politieke debat hoe de gezondheidszorg voor migranten het best geregeld kan worden en het terughoudende beleid van lokale en nationale overheden, maken de zorg voor vluchtelingen moeilijk. Tot nu toe heeft het nog niet geleid tot een uniform beleid in Europa. Momenteel is het aantal vluchtelingen dat Europa probeert te bereiken afgenomen en daarmee is het politieke debat over dit onderwerp meer naar de achtergrond verdwenen. Migratie is echter een fenomeen van alle tijden. Hoewel beleidsplannen voor de zorg en opvang van migranten grotendeels op een nationaal niveau of internationaal niveau gemaakt moet worden, hebben gezondheidsmedewerkers echter een unieke

taak om gezondheid van vluchtelingen te bevorderen. Het contact dat medische professionals hebben met vluchtelingen kan ook helpen bij de integratie van migranten in de samenleving. Deze individuele bijdragen, hoewel wellicht klein, zullen hopelijk de zorg voor migranten verbeteren. Onderzoek kan hierin helpen om de preventie en behandeling van infectieziekten te verbeteren.

DANKWOORD

‘Onderzoek is niks voor mij, maar ik wil het wel eens proberen’

– Sofanne Ravensbergen, Januari 2015…

…en nu, een dankwoord.

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ABOUT THE AUTHOR

Sofia Jacobine (Sofanne) Ravensbergen was born on April 23th in 1992 in Rijnsburg, The Netherlands. She grew up with her parents and brother. Upon graduation from Sint Adelbert College in Wassenaar in 2010, she went to Ghana for 6 months as a volunteer in a community for mentally and physically disabled children. Sofanne started studying medicine at the University of Groningen in September 2011. During her bachelor's degree she was active in different committees of the Medical Faculty Association Panacea. She was part on their board in 2014. In the beginning of 2015, she started to work on a research project on infectious diseases and multidrug resistant microorganisms (MDROs) in asylum seekers. This project would later serve as a basis for her MD/PhD track application which was granted in 2016. In the beginning of her MD/PhD programme, she continued her work on the topic of MDROs in asylum seekers. Laboratory work for this programme was undertaken at the department of Medical Microbiology and Infection prevention in the University Medical Center Groningen (UMCG). Furthermore, she focussed on the topic of screening and vaccination policies for infectious diseases among asylum seekers. She collaborated with the Primary Health Care Centre for Asylum Seekers (GCA) and the department of Infectious Diseases and Immunity, London. Fieldwork was undertaken at the Structure of Welcoming and Hosting of Refugees, Schisto, Athens, Vluchtelingenwerk, the tuberculosis center and department of Internal Medicine of the UMCG. Her clinical training was conducted at the UMCG and Medisch Spectrum Twente, Enschede. Her differentiation clerkship was conducted at the Intensive Care Unit, Martini Ziekenhuis, Groningen and the Department of Internal Medicine, Agogo Presbysterian Hospital, Ghana. She obtained her medical degree in 2019. During the final year of her MD/PhD programme, she collaborated with the Kumasi Centre for Collaborative Research in Tropical Medicine, the Presbyterian Hospital Agogo, and Komfo Anokye Teaching hospital during a stay in Ghana. The above will hopefully provide a basis for her scientific career in infectious diseases and global health. Upon completion of her academic thesis, she is working as a clinical doctor at the department of Internal Medicine at the Scheper Ziekenhuis, Emmen.

LIST OF PUBLICATIONS

1. **Ravensbergen SJ**, Louka C, Lokate M, Bathoorn E, Pournaras S, van der Werf TS, de Lange WC, Stienstra Y, Akkerman OW. Case report: Carbapenemase-producing enterobacteriaceae in an asylum seeker with multidrug-resistant tuberculosis. *Am J Trop Med Hyg*. 2018;98(2):376-378.

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4. **Ravensbergen SJ**, Lokate M, Cornish D, Kloeze E, Ott A, Friedrich AW, van Hest R, Akkerman OW, de Lange WC, van der Werf TS, Bathoorn E, Stienstra Y. High Prevalence of Infectious Diseases and Drug-Resistant Microorganisms in Asylum Seekers Admitted to Hospital; No Carbapenemase Producing Enterobacteriaceae until September 2015. *PLoS One*. 2016;11(5):e0154791.

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9. Beeres DT, **Ravensbergen SJ**, Heidema A, Cornish D, Vonk M, Wijnholds LD, Hendriks JJH, Kleinnijenhuis J, Omansen TF, Stienstra Y. Efficacy of ivermectin mass-drug administration to control scabies in asylum seekers in the Netherlands: A retrospective cohort study between January 2014 – March 2016. *PLoS Negl Trop Dis*. 2018;12(5):e0006401.

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Other publications

11. Hargreaves S, **Ravensbergen SJ**, Nellums LB, Friedland JS, Stienstra Y. "How can we improve the vaccination of underimmunized migrants to Europe?" *WHO Migration & Health Newsletter*, 2019; Spring:5-7.